# EXHIBIT J

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:

Box Issue Fee
Assistant Commissioner for Patents
Washington, D.C. 20231

On Sept. 18, 2000

TOWNSEND and TOWNSEND and CREW LLP

By: Lynda Rolnick

OIPE JC74 SEP 26 2000 PATENT & TRADEMARK OFFICE

PATENT
Attorney Docket No.: 18547-000112US
Client Reference No.: 1000.1B5

23/f
enlarge
7-10-01

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re application of: | Examiner: J. Riley |
| Pirrung et al. | Art Unit: 1634 |
| Application No.: 09/129,470 | Batch No.: N98 |
| Filed: August 4, 1998 | AMENDMENT AFTER ALLOWANCE UNDER 37 CFR § 1.312(a) |
| For: VERY LARGE SCALE IMMOBILIZED POLYMER SYNTHESIS | |

OK TO ENTER
9/19/01 JR

**Box Issue Fee**
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Notice of Allowance mailed , please amend the above-identified application as follows:

In the specification

At p. 51, line 11, please delete "color-coded for" and replace it with --versus--.

At p. 51, line 14, please delete "color".

At p. 52, line 13, please delete ", according to the color coding."

At p. 53, line 22, please delete "color coding" and replace it with --scale--.

Match and Return

In the claims

Please amend the claims as follows. Unamended claims are shown in small type for ease of reference.

123. (Amended) A method of synthesizing a plurality of different polymers on a surface of a substrate, comprising:

(a) providing a substrate having a surface bearing multiple copies of a protective group removable on exposure to an electric field or electric current;

(b) applying the electric field or electric current to the substrate to remove a protective group from a first known location on the surface of the substrate;

c) exposing the surface of the substrate to a first protected monomer bearing a protective group removable on exposure to an electric field or electric current, whereby the protected monomer attaches to the first known location;

(d) applying the electric field or electric current to the substrate to remove a protective group from a second known location on the surface of the substrate;

(e) exposing the surface of the substrate to a second protective monomer bearing a protective group removable on exposure to an electric field or electric current, whereby the second protected monomer attached to the second known location;

(f) repeating (b)-(e) while controlling the known locations on the surface of the substrate to synthesize a plurality of different polymers at known locations on the surface of a substrate.

124. The method of claim 123, wherein the first and second polymers are peptides.

125. The method of claim 123, wherein the first and second polymers are nucleic acids.

126. The method of claim 123, wherein the first and second known locations each have areas of less than 1 $cm^2$.

127. The method of claim 123, further comprising exposing the substrate bearing the plurality of polymers to a receptor, and determining which polymers bind to the receptor.

128. The method of claim 123, wherein the substrate is a material selected from the group consisting of polymerized Langmuir-Blodgett film, functionalized glass, germanium, silicon, polymers, polytetrafluorethylene, polystyrene, gallium arsenide, and combinations thereof.

129. The method of claim 123, wherein the surface of the substrate is flat.

130. The method of claim 123, wherein the known locations are wells in the surface of the substrate.

131. The method of claim 127, wherein the receptor is a nucleic acid.

132. The method of claim 123, wherein the substrate is a polymerized Langmuir Blodgett film, functionalized glass, Si, Ge, GaAs, GaP, SiO2, SiN4, modified silicon, polytetrafluoroethylene, polyvinylidenedifluoride, polystyrene, polycarbonate, flat glass, or single-crystal silicon with surface relief features of less than 10 angstroms, or combinations thereof.

Remarks

Claim 123 has been amended to recite "electric current" as an alternative to "electric field" in accordance with the specification, which uses both of these terms (see e.g., p. 16, lines 22-25). Although the two terms are not necessarily precisely synonymous, they are submitted to be substantial equivalents in the context of the presently claimed methods. Thus, this amendment does not affect the merits.

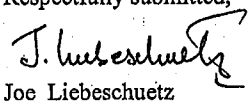
Formal drawings are being provided in black & white form rather than the color form in which some of the drawings were originally submitted. It is submitted that the black & white drawings sufficiently disclose the invention.

Additionally, Applicant would like to notify the Examiner of *inter partes* that relate to the present application. Two commonly owned patents US 5,744,305 and US 5,800,992 have been involved in interference proceedings. Specifically, the interferences were Interference No. 104,359 between commonly owned US 5,744,305 and Brown et al., USSN 08/688,488, and Interference No. 104,358 between commonly owned US 5,800,992 and USSN 08/514,875. Both interferences have been decided (subject to current appeal in District Court of Northern California, Civil Case No. C99 21111-JF/EAI) by the USPTO in favor of real party in interest

Affymetrix, the assignee of the present application. The Junior party challenged the patents on the basis of lack of enablement and written description under 35 USC §112, among other issues. The Junior party's initial position is set out in papers (with supporting information) entitled "Request for Declaration of Interference, 37 C.F.R. §1.608" in both interferences. The initial response of Senior party Patentee is set out in papers (with supporting information) entitled "Fodor's Opposition to Brown's Rule 608(b) Request" in both interferences.

Further, US 5,744,305 and US 5,800,992 are the subject of litigation (*Affymetrix, Inc. v. Hyseq, Inc.*, US District Court for the Northern District of California, San Francisco Division, Civil Action No. C98-03192 FMS, and *Affymetrix. v. Synteni, Inc. and Incyte Pharmaceuticals, Inc.*, US District Court for the Northern District of California, San Francisco, Case No. C98-4508 FMS (MEJ)). In the course of these proceedings, allegations of invalidity over prior art, lack of enablement, lack of support and inequitable conduct (relating to duty of candor, content of declarations under 37 CFR §1.132, and arguments made during prosecution) have been raised. These allegations are denied. Further, oppositions have been filed against a related European application EP 619,321 in the European Patent Office, and a revocation proceeding has been brought in the United Kingdom against related patents GB 2,248,840 and EP (UK) 0 619 321. Collectively, these proceedings have generated a considerable number of references, which were cited on the information disclosure statement and CDs filed above. Applicant can provide copies of litigation documents that may be of interest to the Examiner, but have not done so due to the extensive nature of the multiple litigation and papers filed therein.

Respectfully submitted,



Joe Liebeschuetz
Reg. No. 37,505

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: (415) 576-0200
Fax: (415) 576-0300
JOL
PA 3097098 v1

# EXHIBIT K

I hereby certify that this correspondence is being delivered by Hand Delivery to:
Box Issue Fee
Assistant Commissioner for Patents
Washington, D.C. 20231

On 8-24-2000

TOWNSEND and TOWNSEND and CREW LLP

By: [signature]

PATENT
Attorney Docket No.: 18547-000181US
Client Reference No.: 1000.1b3

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re application of: STEPHEN P.A. FODOR | Examiner: J. Riley |
| Application No.: 08/456,598 | Art Unit: 1656 |
| Filed: June 1, 1995 | Batch No.: Q20 |
| For: VERY LARGE SCALE IMMOBILIZED POLYMER SYNTHESIS | AMENDMENT AFTER ALLOWANCE UNDER 37 CFR §1.312(a) AND COMMUNICATION |

RECEIVED
TECH CENTER 1600/2900
00 NOV 24 PM 2:45

**Box Issue Fee**
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Notice of Allowance mailed August 1, 2000, please amend the above-identified application as follows:

In the specification

At p. 51, line 11, please delete "color-coded for" and replace it with --versus--.

At p. 51, line 14, please delete "color".

At p. 52, line 13, please delete ", according to the color coding".

At p. 53, line 22, please delete "color coding" and replace it with --scale--.

In the claims

116. (Twice amended) The apparatus as recited in claim 108, wherein each of said different oligonucleotide sequences is in a known location [on] on said surface of said substrate has an area of less than 10,000 $\mu m^2$.

Remarks

Formal drawings are being provided in black & white form rather than the color form in which some of the drawings were originally submitted. It is believed that the black & white drawings sufficiently disclose the invention.

The amendment to claim 116 corrects an obvious typographic error present in claim 116.

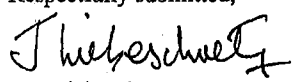
Further, as previously discussed with the Examiner, and indicated on the information disclosure statement dated August 9, 1999, there have been inter party matters that relate to the present application. Two commonly owned patents US 5,744,305 and US 5,800,992 have been involved in interference proceedings. Specifically, the interferences were Interference No. 104,359 between commonly owned US 5,744,305 and Brown et al., USSN 08/688,488, and Interference No. 104,358 between commonly owned US 5,800,992 and USSN 08/514,875. Both interferences have been decided (subject to current appeal in District Court of Northern California, Civil Case No. C99 21111-JF/EAI) by the USPTO in favor of real party in interest Affymetrix, the assignee of the present application. The Junior party challenged the patents on the basis of lack of enablement and written description under 35 USC §112, among other issues. The Junior party's initial position is set out in papers (with supporting information) entitled "Request for Declaration of Interference, 37 C.F.R. §1.608" in both interferences. The initial response of Senior party Patentee is set out in papers (with supporting information) entitled "Fodor's Opposition to Brown's Rule 608(b) Request" in both interferences.

Further, US 5,744,305 and US 5,800,992 are the subject of litigation (Affymetrix, Inc. v. Hyseq, Inc., US District Court for the Northern District of California, San Francisco Division, Civil Action No. C98-03192 FMS, and Affymetrix. v. Synteni, Inc. and Incyte Pharmaceuticals, Inc., US District Court for the Northern District of California, San Francisco, Case No. C98-4508 FMS (MEJ)). In the course of these proceedings, allegations of invalidity over prior art, lack of enablement, lack of support and inequitable conduct (relating to duty of candor, content of declarations under 37 CR §1.132, and arguments made during prosecution) have been raised. These allegations are denied. Further, oppositions have been filed against a related European application EP 619,321 in the European Patent Office, and a revocation proceeding has been brought in the United Kingdom against related patents GB 2,248,840 and EP (UK) 0 619 321. Collectively, these proceedings have generated a considerable number of references, which were cited on the information disclosure statement and CDs filed above.

Applicants can provide copies of litigation documents that may be of interest to the Examiner, but have not done so due to the extensive nature of the multiple litigation and papers filed therein.

The above amendments to the specification and claims merely serve to delete references to color drawings or correct typographical errors and do not touch the merits or add new matter.

Respectfully submitted,



Joe Liebeschuetz
Reg. No. 37,505

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel.: (650) 326-2400
Fax: (650) 326-2422
JOL:llr
PA 3090975 v1

# EXHIBIT L

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

#7/ JR
08/12/99

In re Patent Application of

**FODOR et al.**

Appln. No. 09/056,927 Group Art Unit: 1634

Filed: April 8, 1998 Examiner: E. Campbell

FOR: A METHOD OF DETECTING NUCLEIC ACIDS (as amended)

* * * * *

August 6, 1999

**INFORMATION DISCLOSURE STATEMENT**

Further to the Amendment of June 11, 1999, Applicants submit herewith copies of references cited in the papers entitled "Initial Disclosure of Prior Art Pursuant to 16-7" which were filed by the defendants in litigation involving U.S. Pat. Nos. 5,445,934, 5,744,305, 5,795,716, and 5,800,992 for the Examiner's consideration. The Examiner's attention is also directed to the copies of these papers filed in Civil Action Nos. C98-03192 FMS, C98-4507FMS, and C98-4508 FMS which were previously submitted. The references are listed on the attached form PTO-1449.

If a first Office Action on the merits has been issued, please consider this information disclosure statement (IDS) in accordance with 37 CFR § 1.97(c) and charge the fee set forth in 37 CFR § 1.17(p) to our Deposit Account No. 03-3975 under Order No. 71180/243375.



This IDS is intended to be in full compliance with the rules. But should the Examiner find any part of its required contents to have been omitted, prompt and early notice to that effect is earnestly solicited, along with additional time pursuant to 37 CFR § 1.97(f), to enable Applicants to comply fully.

Consideration of the foregoing and enclosures are earnestly requested.

Additionally, return of a copy of the enclosed Form PTO-1449 with the Examiner's initials in the left column per M.P.E.P. § 609 are earnestly solicited.

Respectfully submitted,

Cushman Darby & Cushman
Intellectual Property Group of
PILLSBURY MADISON & SUTRO

Gary Laigaard Reg No 43,180
for Paul N. Kokulis
Reg. No. 16,773
Tel: (202) 861-3503
Fax: (202) 822-0944

PNK/GRT:maf
Enclosures
1100 New York, Avenue, N.W.
Ninth Floor, East Tower
Washington, D.C. 20005-3918
Tel: (202) 861-3000

# EXHIBIT M

Robert P Taylor (State Bar No. 46046)
Teresa M. Corbin (State Bar No. 132360)
V. Randall Gard (State Bar No. 151677)
N. Thane Bauz (State Bar No. 188439)
HOWREY & SIMON
301 Ravenswood Avenue
Menlo Park, CA 94025
(650) 463-8100

COUNSEL FOR DEFENDANTS
SYNTENI, INC. AND INCYTE
PHARMACEUTICALS, INC.



**IN THE UNITED STATES DISTRICT COURT**
**FOR THE NORTHERN DISTRICT OF CALIFORNIA**
**SAN FRANCISCO**

| | |
|---|---|
| AFFYMETRIX, INC.,<br><br>Plaintiff and counterdefendant,<br><br>v.<br><br>SYNTENI, INC. and INCYTE PHARMACEUTICALS, INC.,<br><br>Defendants and counterplaintiffs. | Case No. C98-4507 FMS (MEJ)<br><br>**INITIAL DISCLOSURE OF PRIOR ART PURSUANT TO 16-7** |

In accordance with Civil L.R. 16-7, Defendants Incyte Pharmaceuticals, Inc. and Synteni, Inc., hereby submit this initial disclosure of prior art developed to date relating to U.S. Patent No. 5,445,934 ('934 Patent). Defendants are actively engaged in searching our other prior art and persons working in the technologies to which the '934 patent relates. Defendants anticipate that such effort may yield additional prior art of comparable relevance to what is disclosed below, and defendants intend to supplement this disclosure as such additional prior art is located.

Prior Art Affecting the Validity of U.S. Patent No. 5,445,934

Defendants' investigation to date has resulted in the identification of the following prior art references that appear, on their face, to anticipate or render obvious Claims 1, 5, 6, 7 and 8 of the '934 Patent. Defendants acknowledge that numerous disputed issues of claim construction may lie ahead, altering significantly the manner in which a determination of patent validity under 35 U.S.C. §§ 102 and 103 would be carried out. Defendants also acknowledge that issues of enablement may affect the scope or relevance of certain prior art. Defendants have accepted the disclosed prior art at face value and have made no attempt, at this preliminary stage, to evaluate the future impact of claim construction and enablement issues that may be presented.

The asserted claims 1, 5, 6, 7 and 8 of the '934 patent when interpreted as broadly as Affymetrix appears to be interpreting them, are invalid under 35 U.S.C. §102 as anticipated by, or under 35 U.S.C. §103 as obvious in view of, the following prior art references.

1. Claims 1, 5, 6, 7 and 8 of the '934 patent are anticipated by Hanahan *et al.* "Plasmid Screening at High Colony Density", Methods in Enzymology 100:333-342 (1983), or obvious in light of Hanahan *et al.* in combination with Arnold, Jr., US 5,362,866 (11/94), Dattagupta et al., EP 0 281 927 A2 (9/88), Frank, *et al.*, "Simultaneous Synthesis and Biological Applications of DNA Fragments: An Efficient and Complete Methodology," Methods in Enzymology 134:221-251 (1987), Groet, *et al.*, US 4,533,682 (5/86), Guire, US 4,973,493 (11/90), Macevicz, US 5,002,867 (5/91), Southern and Maskos, WO 90/03382 (4/90), Urdea et al, US 4,517,338 (5/85), Dattagupta et al., US 5,348,855 (9/94), Drmanac et al., US 5,202,231 (8/93), Eggers, *et al.*, US 5,532,128 (7/96), Erlich et al., EP 0 237 362 B1 (9/87), Khrapko et al., "An Oligonucleotide Hybridization Approach to DNA Sequencing," FEB 256:118-122 (1989), Khrapko et al., "Hybridization of DNA with Oligonucleotides Immobilized in Gel," Molecular Biology 25:581-591 (1991), Lysov et al., "A New Method For Determining the DNA Nucleotide Sequence By Hybridization With Oligonucleotides," Doklady Biochemistry 303:355-452 (1988), Palva et al., GB 2 156 074A (10/85), Potter, US 4,613,566 (9/86), Saiki and Erlich, WO 89/11548 (11/89), Southern, US 5,700,637 (12/97), Southern, WO 89/10977 (11/89), and/or Wang et al., US 4,925,785 (5/90).

2. Claims 1, 5, 6, 7 and 8 of the '934 patent are anticipated by Southern USP 5,700,637 (12/97), or obvious in light of Southern in combination with Cozzette et al., US 5,200,051 (4/93), Hayes et al., US 4,877,745 (10/89), Kimura et al., "An Immobilized Enzyme Membrane Fabrication Method Using an Ink Jet Nozzle," Biosensors 40:41-52 (1988), Kuriyama, JP Sho 63-223557 (9/88), Miyagi et al., JP 59-24244 (2/84), Madou et al., US 4,874,500 (10/89), Arnold, Jr., US 5,362,866 (11/94), Damagupta et al., EP 0 281 927 A2 (9/88), Frank, *et al.*, "Simultaneous Synthesis and Biological Applications of DNA Fragments: An Efficient and Complete Methodology," *Methods in Enzymology* 134:221-251 (1987), Groet, *et al.*, US 4,533,682 (5/86), Guire, US 4,973,493 (11/90), Macevicz, US 5,002,867 (5/91), Southern and Maskos, WO 90/03382 (4/90), Urdea et al, US 4,517,338 (5/85), Damagupta et al., US 5,348,855 (9/94), Drmanac et al., US 5,202,231 (8/93), Eggers, *et al.*, US 5,532,128 (7/96), Erlich et al., EP 0 237 362 B1 (9/87), Khrapko et al., "An Oligonucleotide Hybridization Approach to DNA Sequencing," FEB 256:118-122 (1989), Khrapko et al., "Hybridization of DNA with Oligonucleotides Immobilized in Gel," Molecular Biology 25:581-591 (1991), Lysov et al., "A New Method For Determining the DNA Nucleotide Sequence By Hybridization With Oligonucleotides," Doklady Biochemistry 303:355-452 (1988), Palva et al., GB 2 156 074A (10/85), Potter, US 4,613,566 (9/86), Saiki and Erlich, WO 89/11548 (11/89), Southern, WO 89/10977 (11/89) and/or Wang et al., US 4,925,785 (5/90).

3. Claims 1, 5, 6, 7 and 8 of the '934 patent are anticipated by Southern WO 89/10977, or obvious in light of Southern in combination with Cozzette et al., US 5,200,051 (4/93), Hayes et al., US 4,877,745 (10/89), Kimura et al., "An Immobilized Enzyme Membrane Fabrication Method Using an Ink Jet Nozzle," Biosensors 40:41-52 (1988), Kuriyama, JP Sho 63-223557 (9/88), Miyagi et al., JP 59-24244 (2/84), Madou et al., US 4,874,500 (10/89), Arnold, Jr., US 5,362,866 (11/94), Damagupta et al., EP 0 281 927 A2 (9/88), Frank, *et al.*, "Simultaneous Synthesis and Biological Applications of DNA Fragments: An Efficient and Complete Methodology," Methods in Enzymology 134:221-251 (1987), Groet, *et al.*, US 4,533,682 (5/86), Guire, US 4,973,493 (11/90), Macevicz, US 5,002,867 (5/91), Southern and Maskos, WO 90/03382 (4/90), Urdea et al, US 4,517,338 (5/85), Damagupta et al., US 5,348,855 (9/94), Drmanac et al., US 5,202,231 (8/93), Eggers, *et al.*, US 5,532,128 (7/96), Erlich et al., EP 0 237 362 B1 (9/87), Khrapko et al., "An

Oligonucleotide Hybridization Approach to DNA Sequencing," FEB 256:118-122 (1989), Khrapko et al., "Hybridization of DNA with Oligonucleotides Immobilized in Gel," Molecular Biology 25:581-591 (1991), Lysov et al., "A New Method For Determining the DNA Nucleotide Sequence By Hybridization With Oligonucleotides," Doklady Biochemistry 303:355-452 (1988), Palva et al., GB 2 156 074A (10/85), Potter, US 4,613,566 (9/86), Saiki and Erlich, WO 89/11548 (11/89), Southern, US 5,700,637 (12/97), and/or Wang et al., US 4,925,785 (5/90).

4. Claims 1, 5, 6, 7 and 8 of the '934 patent are anticipated by Eggers *et al* USP 5,532,128 (7/96), or obvious in light of Eggers in combination with Cozzette et al., US 5,200,051 (4/93), Hayes et al., US 4,877,745 (10/89), Kimura et al., "An Immobilized Enzyme Membrane Fabrication Method Using an Ink Jet Nozzle," Biosensors 40:41-52 (1988), Kuriyama, JP Sho 63-223557 (9/88), Miyagi et al., JP 59-24244 (2/84), Madou et al., US 4,874,500 (10/89), Arnold, Jr., US 5,362,866 (11/94), Damagupta et al., EP 0 281 927 A2 (9/88), Frank, *et al.*, "Simultaneous Synthesis and Biological Applications of DNA Fragments: An Efficient and Complete Methodology," Methods in Enzymology 134:221-251 (1987), Groet, *et al.*, US 4,533,682 (5/86), Guire, US 4,973,493 (11/90), Macevicz, US 5,002,867 (5/91), Southern and Maskos, WO 90/03382 (4/90), Urdea et al, US 4,517,338 (5/85), Damagupta et al., US 5,348,855 (9/94), Drmanac et al., US 5,202,231 (8/93), Erlich et al., EP 0 237 362 B1 (9/87), Khrapko et al., "An Oligonucleotide Hybridization Approach to DNA Sequencing," FEB 256:118-122 (1989), Khrapko et al., "Hybridization of DNA with Oligonucleotides Immobilized in Gel," Molecular Biology 25:581-591 (1991), Lysov et al., "A New Method For Determining the DNA Nucleotide Sequence By Hybridization With Oligonucleotides," Doklady Biochemistry 303:355-452 (1988), Palva et al., GB 2 156 074A (10/85), Potter, US 4,613,566 (9/86), Saiki and Erlich, WO 89/11548 (11/89), Southern, US 5,700,637 (12/97), Southern, WO 89/10977 (11/89), and/or Wang et al., US 4,925,785 (5/90).

5. Claims 1, 5, 6, 7 and 8 of the '934 patent are anticipated by Khrapko et al., "An Oligonucleotide Hybridization Approach to DNA Sequencing," FEB 256:118-122 (1989), or obvious in light of Khrapko in combination with Cozzette et al., US 5,200,051 (4/93), Hayes et al., US 4,877,745 (10/89), Kimura et al., "An Immobilized Enzyme

Membrane Fabrication Method Using an Ink Jet Nozzle," Biosensors 40:41-52 (1988), Kuriyama, JP Sho 63-223557 (9/88), Miyagi et al., JP 59-24244 (2/84), Madou et al., US 4,874,500 (10/89), Arnold, Jr., US 5,362,866 (11/94), Dattagupta et al., EP 0 281 927 A2 (9/88), Frank, *et al.*, "Simultaneous Synthesis and Biological Applications of DNA Fragments: An Efficient and Complete Methodology," Methods in Enzymology 134:221-251 (1987), Groet, *et al.*, US 4,533,682 (5/86), Guire, US 4,973,493 (11/90), Macevicz, US 5,002,867 (5/91), Southern and Maskos, WO 90/03382 (4/90), Urdea et al, US 4,517,338 (5/85), Dattagupta et al., US 5,348,855 (9/94), Drmanac et al., US 5,202,231 (8/93), Eggers, *et al.*, US 5,532,128 (7/96), Erlich et al., EP 0 237 362 B1 (9/87), Khrapko et al., "Hybridization of DNA with Oligonucleotides Immobilized in Gel," Molecular Biology 25:581-591 (1991), Lysov et al., "A New Method For Determining the DNA Nucleotide Sequence By Hybridization With Oligonucleotides," Doklady Biochemistry 303:355-452 (1988), Palva et al., GB 2 156 074A (10/85), Potter, US 4,613,566 (9/86), Saiki and Erlich, WO 89/11548 (11/89), Southern, US 5,700,637 (12/97), Southern, WO 89/10977 (11/89), and/or Wang et al., US 4,925,785 (5/90).

6. Claims 1, 5, 6, 7 and 8 of the '934 patent are anticipated by Drmanac et al., US 5,202,231 (8/93), or obvious in light of Drmanac in combination with Cozzette et al., US 5,200,051 (4/93), Hayes et al., US 4,877,745 (10/89), Kimura et al., "An Immobilized Enzyme Membrane Fabrication Method Using an Ink Jet Nozzle," Biosensors 40:41-52 (1988), Kuriyama, JP Sho 63-223557 (9/88), Miyagi et al., JP 59-24244 (2/84), Madou et al., US 4,874,500 (10/89), Arnold, Jr., US 5,362,866 (11/94), Dattagupta et al., EP 0 281 927 A2 (9/88), Frank, *et al.*, "Simultaneous Synthesis and Biological Applications of DNA Fragments: An Efficient and Complete Methodology," Methods in Enzymology 134:221-251 (1987), Groet, *et al.*, US 4,533,682 (5/86), Guire, US 4,973,493 (11/90), Macevicz, US 5,002,867 (5/91), Southern and Maskos, WO 90/03382 (4/90), Urdea et al, US 4,517,338 (5/85), Dattagupta et al., US 5,348,855 (9/94), Khrapko et al., "An Oligonucleotide Hybridization Approach to DNA Sequencing," FEB 256:118-122 (1989), Eggers, *et al.*, US 5,532,128 (7/96), Erlich et al., EP 0 237 362 B1 (9/87), Khrapko et al., "Hybridization of DNA with Oligonucleotides Immobilized in Gel," Molecular Biology 25:581-591 (1991), Lysov et al., "A New Method For Determining the DNA Nucleotide Sequence By Hybridization With Oligonucleotides," Doklady

Biochemistry 303:355-452 (1988), Palva et al., GB 2 156 074A (10/85), Potter, US 4,613,566 (9/86), Saiki and Erlich, WO 89/11548 (11/89), Southern, US 5,700,637 (12/97), Southern, WO 89/10977 (11/89), and/or Wang et al., US 4,925,785 (5/90).

7. Claims 1, 5, 6, 7 and 8 of the '934 patent are anticipated by Drmanac et al., Yugoslav Patent No. 570/87 (2/88), or obvious in light of Drmanac in combination with Cozzette et al., US 5,200,051 (4/93), Hayes et al., US 4,877,745 (10/89), Kimura et al., "An Immobilized Enzyme Membrane Fabrication Method Using an Ink Jet Nozzle," Biosensors 40:41-52 (1988), Kuriyama, JP Sho 63-223557 (9/88), Miyagi et al., JP 59-24244 (2/84), Madou et al., US 4,874,500 (10/89), Arnold, Jr., US 5,362,866 (11/94), Damagupta et al., EP 0 281 927 A2 (9/88), Frank, *et al.*, "Simultaneous Synthesis and Biological Applications of DNA Fragments: An Efficient and Complete Methodology," Methods in Enzymology 134:221-251 (1987), Groet, *et al.*, US 4,533,682 (5/86), Guire, US 4,973,493 (11/90), Macevicz, US 5,002,867 (5/91), Southern and Maskos, WO 90/03382 (4/90), Urdea et al, US 4,517,338 (5/85), Damagupta et al., US 5,348,855 (9/94), Khrapko et al., "An Oligonucleotide Hybridization Approach to DNA Sequencing," FEB 256:118-122 (1989), Eggers, *et al.*, US 5,532,128 (7/96), Erlich et al., EP 0 237 362 B1 (9/87), Khrapko et al., "Hybridization of DNA with Oligonucleotides Immobilized in Gel," Molecular Biology 25:581-591 (1991), Lysov et al., "A New Method For Determining the DNA Nucleotide Sequence By Hybridization With Oligonucleotides," Doklady Biochemistry 303:355-452 (1988), Palva et al., GB 2 156 074A (10/85), Potter, US 4,613,566 (9/86), Saiki and Erlich, WO 89/11548 (11/89), Southern, US 5,700,637 (12/97), Southern, WO 89/10977 (11/89), and/or Wang et al., US 4,925,785 (5/90).

8. Claims 1, 5, 6, 7 and 8 of the '934 patent are anticipated by Lysov et al., "A New Method For Determining the DNA Nucleotide Sequence By Hybridization With Oligonucleotides," Doklady Biochemistry 303:355-452 (1988) or obvious in light of Lysov in combination with Cozzette et al., US 5,200,051 (4/93), Hayes et al., US 4,877,745 (10/89), Kimura et al., "An Immobilized Enzyme Membrane Fabrication Method Using an Ink Jet Nozzle," Biosensors 40:41-52 (1988), Kuriyama, JP Sho 63-223557 (9/88), Miyagi et al., JP 59-24244 (2/84), Madou et al., US 4,874,500 (10/89),

Arnold, Jr., US 5,362,866 (11/94), Damagupta et al., EP 0 281 927 A2 (9/88), Frank, *et al.*, "Simultaneous Synthesis and Biological Applications of DNA Fragments: An Efficient and Complete Methodology," Methods in Enzymology 134:221-251 (1987), Urdea, *et al.*, US 4,533,682 (5/86), Guire, US 4,973,493 (11/90), Macevicz, US 5,002,867 (5/91), Southern and Maskos, WO 90/03382 (4/90), Urdea et al, US 4,517,338 (5/85), Damagupta et al., US 5,348,855 (9/94), Drmanac et al., US 5,202,231 (8/93), Eggers, *et al.*, US 5,532,128 (7/96), Erlich et al., EP 0 237 362 B1 (9/87), Khrapko et al., "Hybridization of DNA with Oligonucleotides Immobilized in Gel," Molecular Biology 25:581-591 (1991), Palva et al., GB 2 156 074A (10/85), Power, US 4,613,566 (9/86), Saiki and Erlich, WO 89/11548 (11/89), Southern, US 5,700,637 (12/97), Southern, WO 89/10977 (11/89), and/or Wang et al., US 4,925,785 (5/90).

9. Claims 1, 5, 6, 7 and 8 of the '934 patent are rendered obvious under 35 U.S.C. 103 in view of Damagupta et al., US 5,348,855 (9/94) in combination with Cozzette et al., US 5,200,051 (4/93), Hayes et al., US 4,877,745 (10/89), Kimura et al., "An Immobilized Enzyme Membrane Fabrication Method Using an Ink Jet Nozzle," Biosensors 40:41-52 (1988), Kuriyama, JP Sho 63-223557 (9/88), Miyagi et al., JP 59-24244 (2/84), Madou et al., US 4,874,500 (10/89), Chang, US 4,591,570 (5/86), Chang, WO 84/03151 (8/84), Clark et al., US 4,728,591 (5/88), Cozzette et al., US 5,200,051 (4/93), Ekins, "Developments In Immunoassay Methods," Biochimica Clinica Suppl. 1/8:13 (1989), Ekins, US 5,432,099 (11/95), Ekins et al., "Fluorescence Spectroscopy and its Application to a New Generation of High Sensitivity, Multi-Microspot, Multianalyte, Immunoassay," Clinica Chimica Acta 194:91-114 (1990), Geysen, WO 84/03564 (9/84), Gordon et al., EP 0 063 810 A1 (11/82), Herzberg and Fish, EP 0 171 150 B1 (2/86), Huang, US 4,327,073 (4/82), Humphries et al., US 4,704,353 (11/87), Johnson, US 4,216,245 (8/80), Kleinfeld et al., "Controlled Outgrowth of Dissociated Neurons on Patterned Substrates," J. Neuroscience 8:4098-4120 (1988), Lowe and Earley, US 4,562,157 (12/85), Madou et al., US 4,874,500 (10/89), Drmanac et al., US 5,202,231 (8/93), Eggers, *et al.*, US 5,532,128 (7/96), Erlich et al., EP 0 237 362 B1 (9/87), Khrapko et al., "An Oligonucleotide Hybridization Approach to DNA Sequencing," FEB 256:118-122 (1989), Khrapko et al., "Hybridization of DNA with Oligonucleotides Immobilized in Gel," Molecular Biology 25:581-591 (1991), Lysov et al., "A New

Method For Determining the DNA Nucleotide Sequence By Hybridization With Oligonucleotides," Doklady Biochemistry 303:355-452 (1988), Palva et al., GB 2 156 074A (10/85), Potter, US 4,613,566 (9/86), Saiki and Erlich, WO 89/11548 (11/89), Southern, US 5,700,637 (12/97), Southern, WO 89/10977 (11/89), and/or Wang et al., US 4,925,785 (5/90).

10. Claims 1, 5, 6, 7 and 8 of the '934 patent are rendered obvious under 35 U.S.C. 103 in view of Wang et al., US 4,925,785 (5/90) in combination with Cozzette et al., US 5,200,051 (4/93), Hayes et al., US 4,877,745 (10/89), Kimura et al., "An Immobilized Enzyme Membrane Fabrication Method Using an Ink Jet Nozzle," Biosensors 40:41-52 (1988), Kuriyama, JP Sho 63-223557 (9/88), Miyagi et al., JP 59-24244 (2/84), Madou et al., US 4,874,500 (10/89), Chang, US 4,591,570 (5/86), Chang, WO 84/03151 (8/84), Clark et al., US 4,728,591 (5/88), Cozzette et al., US 5,200,051 (4/93), Elcins, "Developments In Immunoassay Methods," Biochimica Clinica Suppl. 1/8:13 (1989), Elcins, US 5,432,099 (11/95), Elcins et al., "Fluorescence Spectroscopy and its Application to a New Generation of High Sensitivity, Multi-Microspot, Multianalyte, Immunoassay," Clinica Chimica Acta 194:91-114 (1990), Geysen, WO 84/03564 (9/84), Gordon et al., EP 0 063 810 A1 (11/82), Herzberg and Fish, EP 0 171 150 B1 (2/86), Huang, US 4,327,073 (4/82), Humphries et al., US 4,704,353 (11/87), Johnson, US 4,216,245 (8/80), Kleinfeld et al., "Controlled Outgrowth of Dissociated Neurons on Patterned Substrates," J. Neuroscience 8:4098-4120 (1988), Lowe and Earley, US 4,562,157 (12/85), Madou et al., US 4,874,500 (10/89), Drmanac et al., US 5,202,231 (8/93), Eggers, *et al.*, US 5,532,128 (7/96), Erlich et al., EP 0 237 362 B1 (9/87), Khrapko et al., "An Oligonucleotide Hybridization Approach to DNA Sequencing," FEB 256:118-122 (1989), Khrapko et al., "Hybridization of DNA with Oligonucleotides Immobilized in Gel," Molecular Biology 25:581-591 (1991), Lysov et al., "A New Method For Determining the DNA Nucleotide Sequence By Hybridization With Oligonucleotides," Doklady Biochemistry 303:355-452 (1988), Palva et al., GB 2 156 074A (10/85), Potter, US 4,613,566 (9/86), Saiki and Erlich, WO 89/11548 (11/89), Southern, US 5,700,637 (12/97), Southern, WO 89/10977 (11/89), and/or Dattagupta et al., US 5,348,855 (9/94).

11. Claims 1, 5, 6, 7 and 8 of the '934 patent are rendered obvious under 35 U.S.C. 103 in view of Saiki *et al.*, "Genetic analysis of amplified DNA with immobilized sequence-specific oligonucleotide probes", *Proc. Natl. Acad. Sci. USA*, 86:6230-6234 (1989), in combination with Cozzette et al., US 5,200,051 (4/93), Hayes et al., US 4,877,745 (10/89), Kimura et al., "An Immobilized Enzyme Membrane Fabrication Method Using an Ink Jet Nozzle," Biosensors 40:41-52 (1988), Kuriyama, JP Sho 63-223557 (9/88), Miyagi et al., JP 59-24244 (2/84), Madou et al., US 4,874,500 (10/89), Chang, US 4,591,570 (5/86), Chang, WO 84/03151 (8/84), Clark et al., US 4,728,591 (5/88), Cozzette et al., US 5,200,051 (4/93), Ekins, "Developments In Immunoassay Methods," Biochimica Clinica Suppl. 1/8:13 (1989), Ekins, US 5,432,099 (11/95), Ekins et al., "Fluorescence Spectroscopy and its Application to a New Generation of High Sensitivity, Multi-Microspot, Multianalyte, Immunoassay," Clinica Chimica Acta 194:91-114 (1990), Geysen, WO 84/03564 (9/84), Gordon et al., EP 0 063 810 A1 (11/82), Herzberg and Fish, EP 0 171 150 B1 (2/86), Huang, US 4,327,073 (4/82), Humphries et al., US 4,704,353 (11/87), Johnson, US 4,216,245 (8/80), Kleinfeld et al., "Controlled Outgrowth of Dissociated Neurons on Patterned Substrates," J. Neuroscience 8:4098-4120 (1988), Lowe and Earley, US 4,562,157 (12/85), Madou et al., US 4,874,500 (10/89), Drmanac et al., US 5,202,231 (8/93), Eggers, *et al.*, US 5,532,128 (7/96), Erlich et al., EP 0 237 362 B1 (9/87), Khrapko et al., "An Oligonucleotide Hybridization Approach to DNA Sequencing," FEB 256:118-122 (1989), Khrapko et al., "Hybridization of DNA with Oligonucleotides Immobilized in Gel," Molecular Biology 25:581-591 (1991), Lysov et al., "A New Method For Determining the DNA Nucleotide Sequence By Hybridization With Oligonucleotides," Doklady Biochemistry 303:355-452 (1988), Palva et al., GB 2 156 074A (10/85), Potter, US 4,613,566 (9/86), Saiki and Erlich, WO 89/11548 (11/89), Southern, US 5,700,637 (12/97), Southern, WO 89/10977 (11/89), and/or Wang et al., US 4,925,785 (5/90).

12. Claims 1, 5, 6, 7 and 8 of the '934 patent are rendered obvious under 35 U.S.C. 103 in view of Humphries et al., US 4,704,353 (11/87) in combination with Dattagupta et al., US 5,348,855 (9/94), Drmanac et al., US 5,202,231 (8/93), Eggers, *et al.*, US 5,532,128 (7/96), Erlich et al., EP 0 237 362 B1 (9/87), Khrapko et al., "An Oligonucleotide Hybridization Approach to DNA Sequencing," FEB 256:118-122 (1989), Khrapko et al.,

"Hybridization of DNA with Oligonucleotides Immobilized in Gel," Molecular Biology 25:581-591 (1991), Lysov et al., "A New Method For Determining the DNA Nucleotide Sequence By Hybridization With Oligonucleotides," Doklady Biochemistry 303:355-452 (1988), Palva et al., GB 2 156 074A (10/85), Potter, US 4,613,566 (9/86), Saiki and Erlich, WO 89/11548 (11/89), Southern, US 5,700,637 (12/97), Southern, WO 89/10977 (11/89), Wang et al., US 4,925,785 (5/90), Arnold, Jr., US 5,362,866 (11/94), Dattagupta et al., EP 0 281 927 A2 (9/88), Frank, *et al.*, "Simultaneous Synthesis and Biological Applications of DNA Fragments: An Efficient and Complete Methodology," Methods in Enzymology 134:221-251 (1987), Groet, *et al.*, US 4,533,682 (5/86), Guire, US 4,973,493 (11/90), Macevicz, US 5,002,867 (5/91), Southern and Maskos, WO 90/03382 (4/90), Urdea et al, US 4,517,338 (5/85), Augenlicht, US 4,981,783 (1/91), Craig et al., "Ordering of Cosmid Clones Covering the Herpes Simplex Virus Type I (HSV-I)" Genome, Nuc. Acids. Res. 18:2653-2660 (1990), Gergen et al., "Filter Replicas and Permanent Collections of Recombinant DNA Plasmids," Nucleic Acids Res. 7:2115-2135 (1979), Gillespie, *et al.*, US 4,483,920, (11/84), Hanahan & Meselson, "Plasmid Screening at High Colony Density," Gene 10:63-67, (1980), Hanahan & Meselson, "Plasmid Screening at High Colony Density," Methods in Enzymology 100:333-342, (1983), Kohara *et al.*, "The Physical Map of the Whole E. coli Chromosome: Application of a New Strategy for Rapid Analysis and Sorting of a Large Genomic Library," Cell 50: 495-508 (1987), and/or White *et al.*, US 4,677,054 (6/87).

13. Claims 1, 5, 6, 7 and 8 of the '934 patent are rendered obvious under 35 U.S.C. 103 in view of Augenlichs, US 4,981,783 (1/91) in combination with Cozzette et al., US 5,200,051 (4/93), Hayes et al., US 4,877,745 (10/89), Kimura et al., "An Immobilized Enzyme Membrane Fabrication Method Using an Ink Jet Nozzle," Biosensors 40:41-52 (1988), Kuriyama, JP Sho 63-223557 (9/88), Miyagi et al., JP 59-24244 (2/84), Madou et al., US 4,874,500 (10/89), Chang, US 4,591,570 (5/86), Chang, WO 84/03151 (8/84), Clark et al., US 4,728,591 (3/88), Cozzette et al., US 5,200,051 (4/93), Ekins, "Developments In Immunoassay Methods," Biochimica Clinica Suppl. 1/8:13 (1989), Ekins, US 5,432,099 (11/95), Ekins et al., "Fluorescence Spectroscopy and its Application to a New Generation of High Sensitivity, Multi-Microspot, Multianalyte, Immunoassay," Clinica Chimica Acta 194:91-114 (1990), Geysen, WO 84/03564 (9/84),

Gordon et al., EP 0 063 810 A1 (11/82), Herzberg and Fish, EP 0 171 150 B1 (2/86), Huang, US 4,327,073 (4/82), Humphries et al., US 4,704,353 (11/87), Johnson, US 4,216,245 (8/80), Kleinfeld et al., "Controlled Outgrowth of Dissociated Neurons on Patterned Substrates," J. Neuroscience 8:4098-4120 (1988), Lowe and Earley, US 4,562,157 (12/85), Madou et al., US 4,874,500 (10/89), Craig et al., "Ordering of Cosmid Clones Covering the Herpes Simplex Virus Type I (HSV-I)" Genome, Nuc. Acids. Res. 18:2653-2660 (1990), Gergen et al., "Filter Replicas and Permanent Collections of Recombinant DNA Plasmids," Nucleic Acids Res. 7:2115-2135 (1979), Gillespie, *et al.*, US 4,483,920, (11/84), Hanahan & Meselson, "Plasmid Screening at High Colony Density," Gene 10:63-67, (1980), Hanahan & Meselson, "Plasmid Screening at High Colony Density," Methods in Enzymology 100:333-342, (1983), Kohara *et al.*, "The Physical Map of the Whole E. coli Chromosome: Application of a New Strategy for Rapid Analysis and Sorting of a Large Genomic Library," Cell 50: 495-508 (1987), White *et al.*, US 4,677,054 (6/87), Arnold, Jr., US 5,362,866 (11/94), Damagupta et al., EP 0 281 927 A2 (9/88), Frank, *et al.*, "Simultaneous Synthesis and Biological Applications of DNA Fragments: An Efficient and Complete Methodology," Methods in Enzymology 134:221-251 (1987), Groet, *et al.*, US 4,533,682 (5/86), Guire, US 4,973,493 (11/90), Macevicz, US 5,002,867 (5/91), Southern and Maskos, WO 90/03382 (4/90), and/or Urdea et al, US 4,517,338 (5/85).

14. Claims 1, 5, 6, 7 and 8 of the '934 patent are rendered obvious under 35 U.S.C. 103 in view of Chang, US 4,591,570 (5/86) in combination with Cozzette et al., US 5,200,051 (4/93), Hayes et al., US 4,877,745 (10/89), Kimura et al., "An Immobilized Enzyme Membrane Fabrication Method Using an Ink Jet Nozzle," Biosensors 40:41-52 (1988), Kuriyama, JP Sho 63-223557 (9/88), Miyagi et al., JP 59-24244 (2/84), Madou et al., US 4,874,500 (10/89), Damagupta et al., US 5,348,855 (9/94), Drmanac et al., US 5,202,231 (8/93), Eggers, *et al.*, US 5,532,128 (7/96), Erlich et al., EP 0 237 362 B1 (9/87), Khrapko et al., "An Oligonucleotide Hybridization Approach to DNA Sequencing," FEB 256:118-122 (1989), Khrapko et al., "Hybridization of DNA with Oligonucleotides Immobilized in Gel," Molecular Biology 25:581-591 (1991), Lysov et al., "A New Method For Determining the DNA Nucleotide Sequence By Hybridization With Oligonucleotides," Doklady Biochemistry 303:355-452 (1988), Palva et al., GB 2 156

074A (10/85), Porter, US 4,613,566 (9/86), Saiki and Erlich, WO 89/11548 (11/89), Southern, US 5,700,637 (12/97), Southern, WO 89/10977 (11/89), Wang et al., US 4,925,785 (5/90), Augenlicht, US 4,981,783 (1/91), Craig et al., "Ordering of Cosmid Clones Covering the Herpes Simplex Virus Type I (HSV-I)" Genome, Nuc. Acids. Res. 18:2653-2660 (1990), Gergen et al., "Filter Replicas and Permanent Collections of Recombinant DNA Plasmids," Nucleic Acids Res. 7:2115-2135 (1979), Gillespie, *et al.*, US 4,483,920, (11/84), Hanahan & Meselson, "Plasmid Screening at High Colony Density," Gene 10:63-67, (1980), Hanahan & Meselson, "Plasmid Screening at High Colony Density," Methods in Enzymology 100:333-342, (1983), Kohara *et al.*, "The Physical Map of the Whole E. coli Chromosome: Application of a New Strategy for Rapid Analysis and Sorting of a Large Genomic Library," Cell 50: 495-508 (1987), White *et al.*, US 4,677,054 (6/87), Arnold, *Jr.*, US 5,362,866 (11/94), Dattagupta et al., EP 0 281 927 A2 (9/88), Frank, *et al.*, "Simultaneous Synthesis and Biological Applications of DNA Fragments: An Efficient and Complete Methodology," Methods in Enzymology 134:221-251 (1987), Gruet, *et al.*, US 4,533,682 (5/86), Guire, US 4,973,493 (11/90), Macevicz, US 5,002,867 (5/91), Southern and Maskos, WO 90/03382 (4/90), and/or Urdea et al, US 4,517,338 (5/85).

The following references show features that illustrate or suggest the combination of a multitude of features that became available at various times to persons of ordinary skill, which features limit or render the claims of the '934 patent anticipated under 35 U.S.C. §102 or obvious under 35 U.S.C. §103.

1. Arnold, WO 85/01051 (3/85)
2. Augenlicht, US 5,569,584 (10/96)
3. Augenlicht, EP 0 337 498 A2 (10/89)
4. Baldwin et al., New Photolabile Phosphate Protecting Groups, Tetrahedron 46:6879-6884 (1990)
5. Barzynski et al, US 3,849,137 (11/74)
6. Brigati, US 4,798,706 (1/89)
7. Dattagupta and Crothers, EP 0 130 523 A2 (1/85)

8. Dattagupta and Rabin, EP 0 228 075 A2 (7/87)

9. Dattagupta et al, EP 0 235 726 A3 (9/87)

10. Dattagupta et al, US 4,713,326 (12/87)

11. Diamond *et al.*, US 4,766,062 (8/88)

12. Dueber et al, EP 0 103 197 A1 (3/84)

13. Ekins and Chu, Multianalyte Microspot Immunoassay-Microanalytical "Compact Disk" of the Future, Clin. Chem. 37:1955-1967 (1991)

14. Elan et al, EP 0 046 083 A2 (2/82)

15. Elings et al, US 4,537,861 (8/85)

16. Erlich et al., Canadian Patent 1 284 931 (6/91)

17. Erlich et al., EP 0 237 362 B1 (9/87)

18. Frank, *et al.*, A new general approach for the simultaneous chemical synthesis of large numbers of oligonucleotides: segmental solid supports, Nuc. Acids. Res. 11:4365-4377, (1983)

19. Fuller et al, US 4,946,942 (8/90)

20. Fusek, US 4,516,833 (5/85)

21. Geysen, WO 86/00991 (2/86)

22. Geysen, WO 86/06487 (11/86)

23. Geysen, US 4,833,092 (5/89)

24. Gillespie, *et al.*, US 4,483,920, (11/84)

25. Gingeras et al., WO 88/01302 (2/88)

26. Goodson and Sheridan, EP 0 238 332 A2 (9/87)

27. Hafeman et al., US 5,164,319 (11/92)

28. Hayes et al., EP 0 268 237 A2 (5/88)

29. Houghten, US 4,631,211 (12/86)

30. Kaplan et al, US 4,981,985 (1/91)

31. Kasahara, EP 0142299 A2 (5/85)

32. Kauer, US 4,762,881 (8/88)

33. Koester and Coull, US 4,923,901 (5/90)

34. Leabeck, EP 0 194 132 A2 (9/88)

35. Longiaru *et al.*, US 5,232,829 (8/93)

36. Macevicz, US 5,002,867 (5/91)

37. Macevicz, WO 90/04652 (5/90)

38. Malcolm and Langdale, WO 86/03782 (7/86)

39. Maskos and Southern, Oligonucleotide hybridisations on glass supports, Nucleic Acids Research 20:1679-1684 (1992)

40. McCray and Trentham, Properties and Uses of Photoreactive Caged Compounds, Ann. Rev. Biophys. Biophys. Chem. 18:239-70 (1989)

41. Mundy, US 4,656,127 (4/87)

42. Nishioka et al., EP 0 328 256 A1 (8/89)

43. Nizetic et al., Construction, Arraying and High Density Screening of Large Insert Libraries of Human Chromosomes X and 21, Proc. Natl. Acad. Sci. USA 88:3233-3237 (1991)

44. Paoni, US 4,269, 933 (5/81)

45. Pirning et al., US 5,143,854 (9/92)

46. Rasult and Dasch, The Line Blot: an immunoassay for monoclonal and other antibodies, J. Immunological Methods 125:57-65 (1989)

47. Schneider *et al.*, US 5,424,188 (6/95)

48. Schnur et al., US 5,079,600 (1/92)

49. Schwartz, US 4,886,741 (12/89)

50. Sibbald, GB 2 196 476 A (4/88)

51. Singer and Lawrence, US 4,888,278 (12/89)

52. Tubata et al, US 4,811,062 (3/89)

53. Takayama et al, US 4,984,100 (1/91)

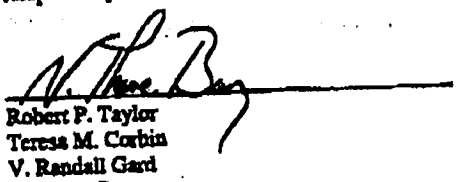
54. Urdea and Warner, EP 0 130 739 A2 (1/85)

55. Urdea et al, US 5,258,506 (11/93)

56. Veldkamp et al, US 4,846,552 (7/89)

Dated: February 26, 1999

Respectfully submitted,



Robert P. Taylor
Teresa M. Corbin
V. Randall Gard
N. Thane Bauz
HOWREY & SIMON
301 Ravenswood Avenue
Menlo Park, CA 94025
(650) 463-8100

COUNSEL FOR DEFENDANTS
SYNTENI, INC. and INCYTE
PHARMACEUTICALS, INC.

# EXHIBIT N

D23

AO6-10-99

CONFIDENTIAL

PUBLIC VERSION II

Robert P. Taylor (State Bar No. 46046)
Teresa M. Corbin (State Bar No. 132360)
V. Randall Gard (State Bar No. 151677)
HOWREY & SIMON
301 Ravenswood Avenue
Menlo Park, CA 94025
(650) 463-8100

COUNSEL FOR DEFENDANTS SYNTENI, INC. AND INCYTE PHARMACEUTICALS, INC.



IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF CALIFORNIA
SAN FRANCISCO

AFFYMETRIX, INC.,

Plaintiff and counterdefendant,

v.

SYNTENI, INC. and INCYTE PHARMACEUTICALS, INC.,

Defendants and counterplaintiffs.

Case No. C98-4508 FMS (MEJ)

**DECLARATION OF MICHAEL C. PIRRUNG**



EXHIBIT
119
PIRRUNG
1/11/06

IAFP00005291

## DECLARATION OF MICHAEL C. PIRRUNG

1. This declaration is based on facts of which I have personal knowledge. If called upon as a witness, I could and would testify to these facts under oath.

2. I was one of the early scientists employed by Affymax, Inc., the predecessor company to Affymetrix. I joined Affymax shortly after it was founded in early 1989. I remained at that company through the end of December 1989, at which time I joined the faculty of Duke University. Even after I left Affymax, I continued to consult with the company, and I visited the company regularly during 1990 and 1991, during which time Affymetrix began to be formed within Affymax. During this time, I was in regular contact with various scientific personnel of Affymax at all levels. I had been offered the job of Director of Chemistry for the company and I was on very good terms with the principals.

3. Since 1990 I have served in the Chemistry Department of Duke University, first as an associate professor and, for the past 5 years, as a full professor and Director of the Duke University Program in Biological Chemistry.

4. I have received a number of honors and awards in my field of study. For example, I have been elected as a fellow of the American Association for the Advancement of Science (1996), I was a John Simon Guggenheim Memorial Foundation Fellow (1994-95), an Alfred P. Sloan Research Fellow (1986-88), and a Fannie and John Hertz Foundation Fellow (1978-80). I have received the Outstanding Young Texas Ex Award from the University of Texas Ex-student's Association (1995), the Intellectual Property Owners Distinguished Inventor Award (1993), the American Association for the Advancement of Science- Newcomb Cleveland Prize (1991) and the Dreyfus Foundation Award for Newly-Appointed Faculty (1982-87). In 1985-90 I was a National Science Foundation Presidential Young Investigator and in 1984-86 I was an Eli Lilly Grantee.

5. I am and have been a Principal Investigator on a number of research grants, including research grants concerning DNA arrays, photochemically-removable groups, DNA synthesis, and combinatorial chemistry.

6. I am currently on the editorial board of the Journal of Combinatorial Chemistry. I serve on the advisory boards of four biotechnology companies and consult with three others.

7. I received a Bachelor of Arts degree in Chemistry with highest honors from the University of Texas, Austin and a Ph.D. in organic chemistry from the University of California, Berkeley. I am an author or co-author of over 100 papers which include technical subject matter relating to the fields of organic and bioorganic chemistry, nucleic acids, combinatorial chemistry, biosynthesis and photochemistry.

8. I am the named inventor on U.S. Patent Nos. 4,851,035 (issued July 25, 1989), 5,143,854 (issued September 1, 1992, and incorporated by reference in U.S. Patent No. 5,800,992), 5,252,743 (issued October 12, 1993), 5,405,783 (issued April 11, 1995), 5,445,934 (issued August 29, 1995), 5,486,633 (issued January 23, 1996) and 5,744,305 (issued April 28, 1998, and the specification of which is incorporated by reference in U.S. Patent No. 5,800,992).

9. I have reviewed U.S. Patent No. 5,800,992 (the '992 patent), a true and correct copy of which is attached hereto. (Exhibit A)

**CAGED BIOTIN**

10. One method identified in the '992 patent for the creation of arrays of compounds is the use of what is referred to as "caged biotin" to immobilize the compounds on a surface at spatially discrete locations. *See the '992 patent*, Col. 27, lines 21-29.

11. The "cage" refers to a molecular structure that prevents biotin from binding to the complementary molecule streptavidin. The cage can be released or deprotected by light. Thus, by selectively exposing caged biotin to light, one is able to create spatially defined regions where biotin is available to bind to streptavidin.

12. In order to make an array, photoprotected ("caged") biotin is first placed on the solid support surface (typically, a glass slide). A photomask is then used to expose the caged biotin in a selected region of the slide to radiated light. This radiated light exposure acts to photochemically remove, or "deprotect," the photolabile protecting group from the caged biotin in that select radiated area. Streptavidin is then washed across the whole surface of the slide and

binds to the deprotected ("uncaged") biotins. Biotinylated compounds of a desired type are then washed across the whole surface of the slide and bind to the streptavidin, thereby immobilizing the compounds onto the selected area of the slide.

13. This process of selective masking, radiated light, photochemical deprotection, streptavidin washing and compound washing is then repeated to immobilize a different compound at another selected area of the slide. In theory, this "step-and-repeat" process can then be performed as many times as needed to immobilize any number of different compounds at specific locations on the glass side. This process is described in various publications. For example, attached hereto are true and correct copies of articles entitled "Step-and-repeat Photopatterning of Protein Features Using Caged-biotin-BSA: Characterization and Resolution." ("Langmuir") (Exhibit B) and "Spatially-Addressable Immobilization of Macromolecules on Solid Supports," ("Sundberg") (Exhibit C ). All six authors of the Sundberg publication have been affiliated with, or employed by, Affymax Research Institute, the predecessor of Affymetrix, Inc., and the predecessor in interest to U.S. Patent Nos. 5,143,854, 5,252,743 and 5,744,305 and the '992 patent.

14. This caged biotin compound immobilization process has been shown to be effective for immobilizing a single compound using a single step of the step-and-repeat process. However, it is clear that subsequent repetitions of the step-and-repeat process cause significantly degraded performance in terms of resolution and contrast of the molecular immobilization. *See Langmuir*. Just because one spatially-directed immobilization can be performed does not mean that tens, hundreds or thousands can be performed in the same way.

15. The problem is that when streptavidin is washed across the slide, it does not bind only to those locations intended by the unmasked regions of the slide where caged biotins have been deprotected by the radiated light. Instead, a significant amount of streptavidin also binds to masked regions of the slide that were not irradiated with light and therefore not intended for binding in that step. *See Langmuir*, p. 4247. This is referred to as "non-specific binding." Then, when the next biotinylated compound wash occurs, some of the compound binds to the

streptavidin at these unintended regions of the slide, in addition to binding to the streptavidin at the intended regions. The significant accumulation of biotinylated compounds binding to unintended regions of the slide with each step rapidly degrades the essential property of the array – the attachment of compounds in spatially discrete regions. Once this property is lost the array cannot function for its intended purpose.

16. This problem becomes evident when, for example, a binding experiment is performed. The purpose of this experiment is to determine to which compound on the array a sample compound binds. A sample compound is fluorescently labeled, washed across the slide and binds to its complementary compound immobilized at the correct regions on the slide. Whether binding to a particular compound has occurred is determined by reading the fluorescent intensity at the region where the compound is supposed to be located. However, if the compound has bound at unintended regions (non-specific binding) this fluorescence is also detected and creates background noise. *See Langmuir*, p. 4247, and *Sundberg*, p. 12054-56. The build up of background noise impairs the ability to read the intended fluorescence signal.

17. This problem is compounded by each repeated iteration of the step-and-repeat caged biotin compound immobilization process. Each iteration causes additional streptavidin to be non-specifically bound at unintended regions across the entirety of the slide. In turn, this causes additional immobilization of compounds at unintended regions across the entirety of the slide. As a result, the background noise level rises for each repeat iteration of the step-and-repeat caged biotin compound immobilization process.

18. For example, a single step of selective masking, radiation, photochemical deprotection, streptavidin washing and compound washing may create a 15% background noise level, which may be a manageable problem. However, the second step will further increase the background noise level across the entirety of the slide. Subsequent steps would continue to raise the background noise level across the entirety of the slide until the contrast ratio between desired signal and background noise becomes one, at which point they essentially become indistinguishable. In the case of a 15% non-specific binding, which is not uncommon, this

complete inability to distinguish signal from background noise could occur after a mere 6 or 7 repeat steps. Hence any array made by such process would be limited to less than 6 or 7 different compounds in order to be minimally functional.

19. There are other steps in the process (caged biotin derivatization of a surface, the cycle of photolithography, streptavidin treatment, addition of the biotinylated molecule), each of which is subject to other errors. Sources of these potential errors include the finite optical density of the lithographic mask, diffraction from the mask interfaces, and non-specific binding of either streptavidin or the molecule to be immobilized.

20. Non-specific binding effectively precludes the use of the caged-biotin immobilization process for even simple arrays, as evidenced by *Sundberg*, p. 12056, wherein it is stated that "[o]ne limitation of the approach is its reliance on serial rounds of photodeprotection and immobilization, which may restrict its application to the creation of fairly simple arrays of biomolecules." This is further supported by the thesis research, performed by Amy Blawas, a doctoral-candidate graduate student on whose thesis committee I served, that shows a pattern of as few as "three fluorescently labeled analytes [being] virtually irresolvable" as stated on page 185 in Amy Blawas' doctoral thesis, a true and correct copy of which is attached hereto (Exhibit D).

**YIELD LIMITATIONS OF PHOTOLITHOGRAPHICALLY CREATED NUCLEOTIDES**

21. I was present at Affymax, Affymetrix' predecessor, when the idea of using photolithographic semiconductor techniques to synthesize biological polymers was first conceived. The principal business objective of Affymax, from its inception, was the synthesis of new drugs. In late 1989, Leighton Read, one of the founders of Affymax, and I discussed the possibility of building new molecules that could be used as drugs. Mr. Read was not a chemist, but he was generally familiar with the photolithography technology used in semiconductor manufacture. I am a chemist, and I was familiar with methods of synthesizing biological molecules. I have also studied photochemical processes since the 1970s and was generally

MOE-10-99

REDACTED

familiar with what might be possible in terms of using light in the process of synthesizing new molecules.

22. Our primary work was directed to the photolithographic synthesis of peptides. Peptides are polymers, similar to proteins in that they are made of amino acids as building blocks, but generally much smaller than proteins. There are 20 known amino acids that can be arranged in an almost infinite number of different combinations to create different compounds in plants and animals. An average protein will contain 150 of these amino acid building blocks, most or all of them (obviously) being used several times within the polymer. Peptides are much simpler than proteins to synthesize, typically containing less than 20 or so amino acid building blocks. Peptides serve a number of biological functions, most notably as hormones (e.g. insulin) and neurotransmitters (e.g. enkephalin). Because of their crucial biological role, peptides are of great interest to researchers seeking to develop new pharmaceuticals.

24. In late 1991 I applied for an NIH grant to find a photoprotection group that would work for the synthesis of nucleic acids (i.e., DNA). One of the reasons for my interest in developing a photoprotective group to use in making DNA was because the photochemistry that we had developed for synthesizing arrays of peptides was unproven in the context of DNA and was not entirely appropriate for making arrays of nucleotides.

NOV-10-05

REDACTED

25. Another method identified in the '992 patent for the preparation of a substrate matrix is parallel *in situ* synthesis of reagents using a process known as Very Large Scale Immobilized Polymer Synthesis (VLSIPS). Much of this description pertains to the synthesis of arrays of peptides and not nucleic acids.

26. As stated above (see ¶ 8), U.S. Patent No. 5,143,854, of which I am a named inventor, is also identified and incorporated by reference in the '992 patent (Column 19, line 59 – Column 20, line 20) as providing VLSIPS methods for synthesizing an array of oligonucleotide probes.

27. For reasons discussed below, one of ordinary skill in the art as of 1990 could not prepare an array of oligonucleotides or polynucleotides, using the VLSIPS synthesis method described, that could be used for gene sequencing or gene expression monitoring applications.

28. As has been shown by Affymetrix' own publications, as recently as 1998, the step-wise yields for probe synthesis are still as low as approximately 90%. For example, attached hereto is a true and correct copy of an article entitled, "The Efficiency of Light-Directed Synthesis of DNA Arrays on Glass Substrates," ("McGall") (Exhibit E) and Chapter 13 of a publication entitled "Molecular Modeling of Nucleic Acids," ("Forman") (Exhibit F). While 90% may appear reasonable, actually it is quite low for oligonucleotide synthesis, where yields below 98% are often considered problematic.

29. A step-wise yield of approximately 90% means that, even today, when one attempts to add an additional nucleotide to the probes being created on the array using the VLSIPS process, only approximately 90% are properly formed. The remaining approximately 10% are failures which are not properly formed and must be "capped" to prevent later addition of unintended nucleotides to the sequence of the probes being formed. These capped probes are thereby prevented from receiving any additional nucleotides and remain forevermore what are referred to as "truncation" probe sequences.

30. This approximately 90% step-wise yield occurs *each time* that one attempts to add another nucleotide base to the sequence of the probes being formed. Therefore, this error rate is compounded with each additional nucleotide added to the probes being formed. As a result, "[t]he proportion of full length probes decreases with nominal length for a given probe site; for example, in 10-mer and 20-mer probe sites only 40% and 15% of the probes are full length, respectively." *See Forman*, page 221.

31. In other words, because only a certain proportion (approximately 90%) of the probes one is attempting to lengthen by an additional nucleotide are properly formed each time one tries to add another nucleotide to the sequence of each probe, the longer the probes one attempts to make the greater the compounding of this failure rate. For example, with the VLSIPS method's step-wise yield of approximately 90%, if one were to attempt to make 100 probes each having a length of 100 nucleotides, essentially none (only about .003% probes) would have the desired length of all 100 nucleotides. The remaining approximately 99.997 probes (essentially all) would be truncated to some lesser number of nucleotides in length.

32. Of course, VLSIPS is typically used to create more than 100 probes at each cell site on an array. However, as described in Affymetrix' own publications, if one attempts to make 14.4 million probes of 100 nucleotides each in a 10 micron by 10 micron area or cell site on an array, only about .003% or 432 probes would have a length of all 100 desired nucleotides. The remaining 14,399,568 probes would be truncated to some lesser number of nucleotides in length. *See Forman*, page 221.

33. The presence of numerous truncated sequences can greatly affect the performance of the arrays. Perhaps the primary effect is simply the depletion of the intended full length sequences that are necessary to unambiguously detect the complementary target sequence in the sample. As is discussed further below, a minimal number of full length probes are required in order to detect hybridization of the target. Clearly the build up of truncations while attempting to create longer full length sequences ultimately sets an upper limit on probe lengths that can be used for hybridization detection on an array.

34. In addition, truncations can hybridize to compounds from the target sample applied to the array. In some cases, this may lead to the fortuitous hybridization to the same sample target compound as the full length probe. However, in many cases the truncation sequence may hybridize to unintended target sequences. This problem may be alleviated to some extent through higher stringency hybridization conditions that favor hybridization of full length probe sequences. However, due to the anomalous hybridization behavior exhibited by VLSIPS probes (*See Forman*), such conditions are difficult if not impossible to achieve. At p. 213, Forman states, "There is little apparent dependence of melting temperatures on probe length or target concentration." What this means is that it is difficult to prevent a short truncation sequence from hybridizing, quite possibly to unintended target sample sequences, at the same time as the intended full length sequence.

35. A still further problem, also evidenced in Affymetrix' own literature, is that "the observed saturating densities of adsorbed target are at most 10% of the predicted densities." *See Forman*, page 221. This means that regardless of the number of probes one can successfully create on the array, only at most 10% of them successfully bind or hybridize to an applied sample. The number of probes successfully created and that successfully bind to targets from an applied sample is thus essentially reduced by a factor of at least 90%. This effectively reduces the 432 correct nucleotides described above (See ¶ 32) to 43 useful probes. As Affymetrix itself admits, "the majority of probes are apparently unavailable to target binding." *See Forman*, page 221.

36. Put simply, using the VLSIPS technology, one may attempt to create as many as 14.4 million probes of a length as short as 100 nucleotides, yet only about 43 of those probes provide any ability to be useful for gene sequencing or gene expression monitoring. This raises serious questions about the ability of VLSIPS technology to create useful probes with lengths beyond very short sequences. Based on Affymetrix' own publications, it appears that the maximum useful probe limit using the VLSIPS photolithographic technology is greater than 20 and less than 50 nucleotides, as explained below.

**THERE IS A PRACTICAL UPPER LENGTH FOR VLSIPS PROBES**

37. The low coupling efficiency of the VLSIPS method results in diminishing numbers of the intended probe sequence with increasing synthesis length. Although one may attempt to synthesize longer and longer probe sequences, ultimately there are too few of the intended probes in each region on the array to allow detection of a fluorescent signal due to hybridization. Thus, the minimum number of probe sequences that can hybridize to their intended target sequence and still yield a detectable fluorescence signal defines a practical upper limit on the length of probes on an array fabricated using the VLSIPS method. This is a limit that is not acknowledged in the patents and publications of Affymetrix related to VLSIPS oligonucleotide arrays. However, using data in a book chapter authored by Affymetrix' own scientists (*See Forman*) I have been able to estimate that a probe length of 50-mer represents a practical upper limit for the VLSIPS arrays. The calculation of this upper limit is detailed below. It is likely that a functional VLSIPS array with 50-mer length probes represents an upper bound that could only be achieved under the most idealized circumstances. Indeed I have reviewed Affymetrix' publications and have found no evidence of arrays with probes longer than 25-mer ever having been fabricated much less used to detect hybridization.

38. In order to determine this upper limit it is necessary to first determine values for the following two parameters:

1) The minimal number of hybridized target sequences that can be accurately detected in the same given area of the array (i.e. the lower limit of hybridization detection).

2) The number of probe molecules in a given area on the array that are capable of hybridizing to the intended target (i.e. the density of functional probe sequences).

39. It is clear that if the value of (2) is less than the value of (1) (i.e. the number of probes capable of hybridizing to the target sequence is less than the detection threshold), it will not be possible to detect target sequences hybridizing to the probes on the array (i.e. the array will not function as required by Claims 4 and 5 of the '992 patent).

40. In order to determine a value for (1) that is most relevant to the detection limits achievable at the time of filing of the patent application which issued as the '992 patent I have referred to statements and experimental data presented in two Affymetrix publications. For example, attached hereto is a true and correct copy of an article entitled, "Matrix DNA Hybridization" ("Sheldon") (Exhibit G), which states on page 719 that: "Experiments suggest a detection limit of <100 fluorescein groups per $\mu m^2$." However, it is not clear that the values cited by Sheldon truly represent the detection of target sequences hybridized to probes on a VLSIPS oligonucleotide array. In contrast, the much later Forman article presents a far more complete analysis including detailed quantitative measurements of the number of probes on a VLSIPS array surface that are involved in hybridization. At p. 211, in the section "Instrumentation and procedures" Forman states that: "The measured adsorbed target densities are estimated to be accurate to +/- 0.2 pmol per $cm^2$." This statement suggests that it is not possible to accurately detect less than 1200 molecules per $\mu m^2$.

41. However, various plots (e.g. Figs. 7-9, and 11) in Forman appear to depict data detected below this 0.2 pmol per $cm^2$ limit (e.g., these figures show data detection in the range of 0.1 pmol per $cm^2$). Of course, based on the stated accuracy there is no certainty that any of these measurements are in fact below this 0.2 pmol per $cm^2$ limit. Therefore, in order to be as generous as possible regarding the VLSIPS technology, I will instead assume for the purposes of these calculations that the limit is +/- 0.02 pmol per $cm^2$ (or 120 molecules per $\mu m^2$) – a ten-fold improvement which would account for any discrepancy between Forman's stated limit and Forman's figures depicting detection at a possibly lower level. Thus, for the purposes of this analysis, I estimated that a detection limit of 120 target sequences per $\mu m^2$ is a reasonable (if not generous) value for (1).

42. In order to calculate a value for (2) I have again referred to Forman. At p.221, Forman states that there is "An initial density of reactive hydroxyl groups of 27 pmol/$cm^2$." This value represents the number of synthesis starting points present on the surface and sets an upper limit of 162,000 probe molecules that can be synthesized in 1 $\mu m^2$. However, also at p. 221,

Forman further notes that typically only 10% of the synthesized oligonucleotide probes on a VLSIPS array are available for hybridization. Consequently, the theoretical upper limit for functional probes in a given area of the array becomes only 16,200 per $\mu m^2$. Finally, using the typical VLSIPS synthesis coupling efficiency of 90% cited by Forman (p. 221), I have calculated and tabulated several values for (2) based on different probe lengths, as shown in the table below.

| Intended Probe Length | Actual Yield Full Length Probes | (2) Number of Functional Probes per $\mu m^2$ |
|---|---|---|
| 10-mer | 35% | 5670 |
| 20-mer | 12% | 1940 |
| 25-mer | 7.2% | 1170 |
| 30-mer | 4.2% | 680 |
| 35-mer | 2.5% | 410 |
| 40-mer | 1.5% | 240 |
| 50-mer | 0.5% | 80 |
| 60-mer | 0.18% | 30 |
| 70-mer | 0.06% | 10 |
| 80-mer | 0.02% | 3 |
| 90-mer | 0.008% | 1 |
| 100-mer | 0.003% | 0.5 |

43. A review of the values for (2) (shown in the right-most column in the table above) shows that they drop below the detection threshold of 120 probes per $\mu m^2$ between the lengths of 40-mer and 50-mer (by calculation a 46-mer is the longest probe length above the threshold).

44. There are a number of parameters one could also consider that would either increase or decrease this upper probe length limit. One factor that would favor an increase in the upper limit of probe length is the behavior of the truncated sequences on the array. Most significant would be those that are 1 to 3 nucleotides shorter than the intended sequence as these would be the most capable of hybridizing to the intended target sequence and thus producing a meaningful signal. Based on Figure 12 in Forman, it appears reasonable to assume that the three longest truncation sequences would increase the final number of functional probes by approximately 30%. Thus the upper limit for probe lengths would increase from a 46-mer to a 49-mer based on the first scenario presented above. It should be noted that the contribution of truncated probe sequences can also have deleterious effects. Due to the fact that truncated sequences do not correspond to the intended probe sequence, it is possible for these sequences to bind to unintended targets and cause incorrect hybridization signals.

45. A number of factors work to decrease the upper probe length limit. Perhaps most significant is the coupling efficiency of 90% cited by Forman. This number is based on studies published in 1997 that utilized the MeNPOC photodeprotective group together with hexaethylene glycol-based linkers for the synthesis of VLSIPS oligonucleotide arrays. Yet there is no description of the use of either of these for VLSIPS oligonucleotide array synthesis in the '992 patent. This is significant because coupling efficiency would be less without these and even a small drop in the coupling efficiency to, for example, 87% would lower the upper probe length limit to a 35-mer.

46. In addition it can be argued that although the detection limit is 120 probes per $\mu m^2$, it is necessary to have at least a two-fold dynamic range of detection for the array to be functional for a differential gene expression assay as claimed by Claims 4 and 5 of the '992 patent. This would push the minimal probe density to 240 per $\mu m^2$ and the upper probe length limit to a 40-mer. Further, because Claims 4 and 5 also require the simultaneous analysis of two differently labeled samples it would be necessary to double the number of available probes in order to ensure detection over this two-fold dynamic range for both samples. Consequently, 480

probes per $\mu m^2$ would be necessary and a 34-mer would represent the upper limit of probe length.

## A CONVERGENCE OF A BROAD RANGE OF TECHNOLOGIES

47. Photolithographic synthesis of nucleotide arrays, as is performed using the VLSIPS technology, and use of those arrays to perform gene sequencing and gene expression monitoring experiments, involves the convergence of a broad range of technical knowledge.

48. The range of technical knowledge required includes at least the following disciplines: 1) Synthetic Organic Chemistry with knowledge of DNA synthesis and organic photochemistry, 2) Physical Chemistry with knowledge of the construction of optical systems, 3) Biophysical Chemistry with knowledge of fluorescence microscopy, 4) Engineering with knowledge in systems integration, 5) Molecular Biology with knowledge of hybridization assays, sample preparation, RNA processing, and labeling, and 6) Computer Science with knowledge of optical system control for mask registration, system control of device interactions, and data analysis for probe sequence selection.

49. DNA synthesis is an unusually demanding chemical synthesis technology, and many years of research in many academic laboratories around the world were required to solve this process. Ultimately, chemical DNA synthesis has become one of the most perfected and reliable of chemical synthesis methodologies (often greater than 99% yield per coupling cycle), primarily based on the chemistry developed in academia and the automated chemical synthesizers developed by instrument manufacturers. But these chemistries and machines work together only in the very specific configuration perfected and intended.

## MANY ASSUMPTIONS ABOUT THE VLSIPS PROCESS PROVED FALSE

50. In spite of such rigid requirements, it was assumed in the late 1980s and early 1990s that many aspects of standard chemical DNA synthesis could simply be transferred and applied to photolithographic DNA synthesis using the VLSIPS approach.

NOV-10-99

REDACTED

51. Before describing the various reasons one could not simply translate what worked in the chemical DNA synthesis process to the photolithographic DNA synthesis process, it is helpful to have at least a basic understanding of the types of interactions that occur between the nucleotide bases in a DNA sequence. Each DNA sequence is actually comprised of two separate strands each comprising a sequence of nucleotides. It is these two strands that combine to form the now-famous "double helix" of DNA. The main features of the Watson-Crick model consist of two antiparallel helical polynucleotide chains coiled around the same axis to form a double helix. Deoxyribose-phosphate backbones are on the outside of the helix and purine and pyrimidine bases lie approximately at right angles to the axis on the inside of the helix. The two chains are held together by hydrogen bonds between pairs of bases, each member of the pair belonging to a different polynucleotide chain. There are four different bases; adenine is always paired with thymine and guanine is always paired with cytosine. The two chains are therefore complementary.

52. To form such a structure, each nucleotide base has three different physical points of connection or interaction. The 5' hydroxyl group ("top" connection) of one nucleotide base connects to the 3' hydroxyl group ("bottom" connection) of another nucleotide base to form the nucleotide sequence. Further, each nucleotide in the sequence (except thymine) can connect via the exocyclic amine ("side" or "auxiliary" connection) to a complementary nucleotide base in another nucleotide sequence to form the DNA double-helix.

53. Importantly, each point of connection or reactivity must be mutually exclusive with each other point of connection on that nucleotide base in order to ensure there is no commonality of connection. Otherwise, for example, the top connection of a nucleotide base might incorrectly connect to the side or auxiliary connection of another base. If such connection occurred, this would prevent the specific structure of the DNA double-helix from forming. The connection points must therefore be controlled in any type of DNA synthesis.

NOV 10 99

REDACTED

54. Various forms of connection point control have been utilized. For example, removable protecting groups are placed on the top connection points to allow addition or connection of another nucleotide to the sequence only when desired. Likewise, nucleoside protecting groups are placed on the side connection points to allow auxiliary connection between sequences only when desired. Lastly, linkers are used to connect the bottom connection points to a solid surface and thereby anchor the nucleotide strand thus preventing additional nucleotides from being added underneath the bottom nucleotide in the strand.

55. While operation and control of such mutually exclusive reactivity of nucleotide bases was understood and achieved in standard chemical DNA synthesis as of 1990, the same cannot be said for photolithographic DNA synthesis.

56. Common practice in chemical DNA synthesis, once the desired sequence has been synthesized, is to wash the glass surface with ammonia under heating conditions. This removes the protective groups on the side connections of the nucleotide bases. This also severs the linker between the first nucleotide in the sequence and the surface to which the sequence is anchored. Severing the linker thus frees the synthesized sequence so that it can be transported to wherever it is intended to be used.

57. With photolithographic DNA synthesis, the synthesized sequence is intended to be used at the site where it is synthesized. In other words, once the sequence has been synthesized at a given location on the array surface, it is intended to remain there. The array may be physically moved elsewhere, but the sequence itself is intended to remain always at the same location on the array. That is why the ammonia wash typically used in chemical DNA synthesis to remove the nucleoside protecting groups cannot be used in photolithographic DNA synthesis.

58. Therefore, by comparison to chemical DNA synthesis, a different bottom connection linker had to be found, a different side connection nucleoside protecting group had to be found, or a different process or mechanism to remove the auxiliary or side connection

MDS-10-99

REDACTED

nucleoside protecting group without severing the bottom connection linker had to be found, in order to implement photolithographic DNA synthesis. For example, attached hereto is a true and correct copy of an article from the journal, "Nucleic Acids Res." (Exhibit H). An effective alternative was apparently unknown to Affymetrix until sometime after 1990, as evidenced by their own publications. For example, attached hereto is a true and correct copy of an article entitled, "Light-generated oligonucleotide arrays for rapid DNA sequence analysis" ("Pease") (Exhibit I). And while Affymax' (Affymetrix' predecessor) experiments did show the ability to form dimers (nucleotide sequences of two bases), thymine was used as the first base of the dimer, which needs no side chain protecting group, and cytidine was used as the second base of the dimer, which had instead of a protecting group a linker that later coupled to a fluorescent tag for the dimer. For example, attached hereto is a true and correct copy of an article entitled, "Light-Directed, Spatially Addressable Parallel Chemical Synthesis" ("Fodor") (Exhibit J). When confronted with the generic problem using all four bases, new solutions were required.

59. Another problem was later discovered when attempting to utilize conventional chemical DNA synthesis approaches in photolithograpic DNA synthesis. In automated chemical DNA synthesis, a benzoyl group is conventionally used as a nucleoside protecting group to cover or protect the nucleotide side connection during DNA synthesis. A benzoyl group is used because it is very stable and somewhat difficult to remove unintentionally.

60. However, by definition, photolithographic DNA synthesis uses ultraviolet (UV) light to perform the synthesis process. This is a problem because UV light destroys the cytidine nucleotide base when it is protected by benzoyl.

61. Affymetrix' own later publications show a shift away from using benzoyl to phenoxyacetyl. *See Pease*. Additionally see an article, a true and correct copy of which is

NOV-10-99

REDACTED

attached hereto, entitled "Comparison of Methods for Photochemical Phosphoramidite-Based DNA Synthesis" ("Pirrung") (Exhibit K).

62. A still further problem was later discovered when attempting to apply conventional chemical DNA synthesis approaches to photolithograpic DNA synthesis. In conventional chemical DNA synthesis, a mild acid is typically used to remove the nucleotide top connection protecting group. However, by definition, photolithographic DNA synthesis uses light to "photoremove" the nucleotide top connection protecting group. And DNA, by its very nature, is light sensitive in that defects can be introduced into DNA merely by the exposure to light. These DNA defects tend to be greatest with the highest energy radiation.

63. The nucleotide top connection point is chemically comprised of an alcohol of ribose. Deprotection of protecting groups known in 1990 for alcohols required high energy radiation. Unfortunately, high energy radiation damages DNA.

64. The search for just such a protecting group was the subject of a Department of Energy grant application I filed in late 1991 wherein I stated that, "No photoremovable groups are available today that are adequate for DNA." Attached hereto is a true and correct copy of my 1991 DOE grant application (Exhibit L).

65. Just as assumptions about the applicability of chemical DNA synthesis to photolithographic DNA synthesis proved incorrect, assumptions about the applicability of photolithographic peptide synthesis to photolithographic DNA synthesis likewise proved incorrect. For example, because peptides have different chemical structure and molecular affinities than do nucleotides, the linker used for peptides proved unusable for DNA synthesis. The linkers used to synthesize peptides on supports end in amines (nitrogens) whereas the linkers used for DNA synthesis end in hydroxyl groups (oxygens).

66. Interestingly, conventional auxiliary protecting groups used for conventional synthesis of peptides proved to work even with photolithographic peptide synthesis. This is in contrast to conventional auxiliary protecting groups used for conventional chemical synthesis of nucleotides which did not work for photolithographic DNA synthesis, as described above. See ¶ 53.

67. However, such was not the case with photoremovable protecting groups when attempting to apply photolithographic peptide synthesis approaches to photolithographic DNA synthesis. In peptide synthesis, the amine group is highly reactive and must be attenuated. A good photodeprotective group to attenuate is the oxycarbonyl group (e.g., MeNPOC). However, in DNA synthesis, the group that is being protected is an alcohol group which is a less reactive functional group than an amine group. This would indicate that one does not need as strong attenuation in DNA synthesis, and that therefore, something like ether should be adequate. However, the ether group that was first used for photolithographic DNA synthesis was the nitroveratryl group which, according to Affymetrix' own publications, proved less than desirable. *See Fodor.*

68.

69. As has become clear from the relevant literature and as explained above, there were numerous incorrect assumptions made about the applicability of conventional chemical DNA synthesis to photolithographic DNA synthesis. Similarly, assumptions about the applicability of photolithographic peptide synthesis to photolithographic DNA synthesis proved misleading and false.

MOS-10-99

REDACTED

70. In retrospect, it is clear that to make a leap from the preparation of peptide arrays by photolithography to DNA arrays, or from conventional chemical DNA synthesis to photolithographic DNA synthesis,

I declare under penalty of perjury that the foregoing is true and correct.

Dated: March 19, 1999

Michael C. Pirrung

# EXHIBIT O

# EXHIBIT REDACTED IN ITS ENTIRETY

# EXHIBIT P

2 M 07.10.99

## TABLE OF CONTENTS



EXHIBIT
121
Pirrung
1/16/06

In a litigation involving two U.S. Patents (Nos. 5,800,992 and 5,744,305) related to the contested patent, Dr. Michael Pirrung, the lead inventor of the contested patent, reveals some of the problems of photolithographic synthesis of polynucleotides at the relevant date (Pirrung (D10), paragraphs 58-70).

> "In retrospect, it is clear that to make a leap from the preparation of peptide arrays by photolithography to DNA arrays, or from conventional chemical DNA synthesis to photolithography DNA synthesis, a number of conceptual and technical advances and revelations were required that were not apparent even to those highly skilled in the arts of peptide and DNA synthesis in 1990".
> (Pirrung (D10), paragraph 70, emphasis added).

More specifically, Dr. Pirrung describes several specific problems of photolithographic synthesis of polynucleotides at the time of filing the contested patent:

> "Another problem was later discovered when attempting to utilize conventional chemical DNA synthesis approaches in photolithographic DNA synthesis. In automated chemical DNA synthesis, a benzoyl group is conventionally used as a nucleoside protecting group to cover or protect the nucleotide side connection during DNA synthesis. A benzoyl group is used because it is very stable and somewhat difficult to remove unintentionally.
>
> However, by definition, photolithographic DNA synthesis uses ultraviolet (UV) light to perform the synthesis process. This is a problem because UV light destroys the cytidine nucleotide base when it is protected by benzoyl. As of 1990, no one knew that benzoylcytidine was destroyed by UV light, presumably because no one had previously had any reason to expose benzoylcytidine to UV light. Therefore, a new protecting group needed to be developed in order for photolithographic DNA synthesis to succeed.
>
> [...]
>
> Deprotection of protecting groups known in 1990 for alcohols required high energy radiation. Unfortunately, high energy radiation damages DNA. So, what was a photoremovable protecting group which would work with lower energy radiation. Identifying this new photoremovable group did not occur until sometimes after 1990 [Pease et al., Proc. Natl. Acad. Sci.

# EXHIBIT Q

US006646243B2

(12) **United States Patent**
**Pirrung et al.**

(10) **Patent No.: US 6,646,243 B2**
(45) **Date of Patent: Nov. 11, 2003**

(54) **NUCLEIC ACID READING AND ANALYSIS SYSTEM**

(75) Inventors: **Michael C. Pirrung**, Durham, NC (US); **J. Leighton Read**, Palo Alto, CA (US); **Stephen P. A. Fodor**, Palo Alto, CA (US); **Lubert Stryer**, Stanford, CA (US)

(73) Assignee: **Affymetrix, Inc.**, Santa Clara, CA (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 18 days.

(21) Appl. No.: **10/098,203**

(22) Filed: **Mar. 15, 2002**

(65) **Prior Publication Data**

US 2003/0013100 A1 Jan. 16, 2003

**Related U.S. Application Data**

(63) Continuation of application No. 09/690,191, filed on Oct. 16, 2000, now Pat. No. 6,403,957, which is a continuation of application No. 09/129,470, filed on Aug. 4, 1998, now Pat. No. 6,329,143, which is a continuation of application No. 08/456,598, filed on Jun. 1, 1995, now Pat. No. 6,225,625, which is a division of application No. 07/954,646, filed on Sep. 30, 1992, now Pat. No. 5,445,934, which is a division of application No. 07/850,356, filed on Mar. 12, 1992, now Pat. No. 5,405,783, which is a division of application No. 07/492,462, filed on Mar. 7, 1990, now Pat. No. 5,143,854, which is a continuation-in-part of application No. 07/362,901, filed on Jun. 7, 1989, now abandoned.

(51) **Int. Cl.**[7] ..... **H01J 40/00**; C12Q 1/68; C07H 21/02

(52) **U.S. Cl.** ..... **250/200**; 250/302; 250/458.1; 250/559.38; 435/6; 435/7.1; 536/22.1; 536/25.32

(58) **Field of Search** ..... 250/200, 302, 250/458.1, 559.38; 435/6, 7.1; 536/22.1, 25.32

(56) **References Cited**

U.S. PATENT DOCUMENTS

| | | | | |
|---|---|---|---|---|
| 3,730,844 | A | 5/1973 | Gilham et al. | 195/103.5 R |
| 3,849,137 | A | 11/1974 | Barzynski et al. | 96/97 |
| 3,862,056 | A | 1/1975 | Hartman | 252/511 |

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

| | | |
|---|---|---|
| CA | 1284931 | 6/1991 |
| DE | 2242394 | 3/1974 |
| DE | 3440141 | 5/1986 |
| DE | 3505287 | 3/1988 |
| EP | 046 083 | 2/1982 |
| EP | 088 636 | 9/1983 |
| EP | 103 197 | 3/1984 |

(List continued on next page.)

OTHER PUBLICATIONS

Bains, "Mixed hybridization and conventional strategies for DNA sequencing," *Genetic Analysis Techniques and Applications*, 10(3–4):84–94 (1993).

Dovichi et al., "DNA sequencing by capillary electrophoresis," *Electrophoresis*, 18:2393–2399 (1997).

Effenhauser et al., "Integrated chip–based capillary electrophoresis," *Electrophoresis*, 18:2203–2213 (1997).

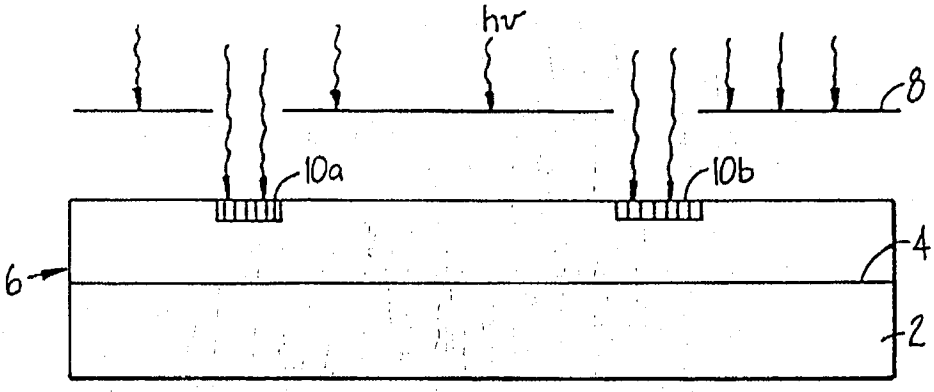
(List continued on next page.)

*Primary Examiner*—Jezia Riley
(74) *Attorney, Agent, or Firm*—Philip McGarrigle

(57) **ABSTRACT**

A method and apparatus for preparation of a substrate containing a plurality of sequences. Photoremovable groups are attached to a surface of a substrate. Selected regions of the substrate are exposed to light so as to activate the selected areas. A monomer, also containing a photoremovable group, is provided to the substrate to bind at the selected areas. The process is repeated using a variety of monomers such as amino acids until sequences of a desired length are obtained. Detection methods and apparatus are also disclosed.

**53 Claims, 22 Drawing Sheets**



# NUCLEIC ACID READING AND ANALYSIS SYSTEM

The present application is a continuation of and claims priority to 09/690,191 filed Oct. 16, 2000 now U.S. Pat. No. 6,403,957 which is a continuation of 09/129,470 filed Aug. 4, 1998 (U.S. Pat. No. 6,329,143) which is a continuation of 08/456,598 filed Jun. 1, 1995 (U.S. Pat. No. 6,225,625), which is a divisional of 07/954,646 filed Sep. 30, 1992 (U.S. Pat. No. 5,445,934), which is a divisional of 07/850,356 filed Mar. 12, 1992 (U.S. Pat. No. 5,405,783) which is a divisional of 07/492,462 filed Mar. 7, 1990 (U.S. Pat. No. 5,143,854), which is a continuation-in-part of 07/362,901 filed Jun. 7, 1989, now abandoned, the disclosures of which are incorporated by reference.

## COPYRIGHT NOTICE



## BACKGROUND OF THE INVENTION

The present inventions relate to the synthesis and placement materials at known locations. In particular, one embodiment of the inventions provides a method and associated apparatus for preparing diverse chemical sequences at known locations on a single substrate surface. The inventions may be applied, for example, in the field of preparation of oligomer, peptide, nucleic acid, oligosaccharide, phospholipid, polymer, or drug congener preparation, especially to create sources of chemical diversity for use in screening for biological activity.

The relationship between structure and activity of molecules is a fundamental issue in the study of biological systems. Structure-activity relationships are important in understanding, for example, the function of enzymes, the ways in which cells communicate with each other, as well as cellular control and feedback systems.

Certain macromolecules are known to interact and bind to other molecules having a very specific three-dimensional spatial and electronic distribution. Any large molecule having such specificity can be considered a receptor, whether it is an enzyme catalyzing hydrolysis of a metabolic intermediate, a cell-surface protein mediating membrane transport of ions, a glycoprotein serving to identify a particular cell to its neighbors, an IgG-class antibody circulating in the plasma, an oligonucleotide sequence of DNA in the nucleus, or the like. The various molecules which receptors selectively bind are known as ligands.

Many assays are available for measuring the binding affinity of known receptors and ligands, but the information which can be gained from such experiments is often limited by the number and type of ligands which are available. Novel ligands are sometimes discovered by chance or by application of new techniques for the elucidation of molecular structure, including x-ray crystallographic analysis and recombinant genetic techniques for proteins.

Small peptides are an exemplary system for exploring the relationship between structure and function in biology. A peptide is a sequence of amino acids. When the twenty naturally occurring amino acids are condensed into polymeric molecules they form a wide variety of three-



dimensional configurations, each resulting from a particular amino acid sequence and solvent condition. The number of possible pentapeptides of the 20 naturally occurring amino acids, for example, is $20^5$ or 3.2 million different peptides. The likelihood that molecules of this size might be useful in receptor-binding studies is supported by epitope analysis studies showing that some antibodies recognize sequences as short as a few amino acids with high specificity. Furthermore, the average molecular weight of amino acids puts small peptides in the size range of many currently useful pharmaceutical products.

Pharmaceutical drug discovery is one type of research which relies on such a study of structure-activity relationships. In most cases, contemporary pharmaceutical research can be described as the process of discovering novel ligands with desirable patterns of specificity for biologically important receptors. Another example is research to discover new compounds for use in agriculture, such as pesticides and herbicides.

Sometimes, the solution to a rational process of designing ligands is difficult or unyielding. Prior methods of preparing large numbers of different polymers have been painstakingly slow when used at a scale sufficient to permit effective rational or random screening. For example, the "Merrifield" method (*J. Am. Chem. Soc.* (1963) 85:2149–2154, which is incorporated herein by reference for all purposes) has been used to synthesize peptides on a solid support. In the Merrifield method, an amino acid is covalently bonded to a support made of an insoluble polymer. Another amino acid with an alpha protected group is reacted with the covalently bonded amino acid to form a dipeptide. After washing, the protective group is removed and a third amino acid with an alpha protective group is added to the dipeptide. This process is continued until a peptide of a desired length and sequence is obtained. Using the Merrifield method, it is not economically practical to synthesize more than a handful of peptide sequences in a day.

To synthesize larger numbers of polymer sequences, it has also been proposed to use a series of reaction vessels for polymer synthesis. For example, a tubular reactor system may be used to synthesize a linear polymer on a solid phase support by automated sequential addition of reagents. This method still does not enable the synthesis of a sufficiently large number of polymer sequences for effective economical screening.

Methods of preparing a plurality of polymer sequences are also known in which a foraminous container encloses a known quantity of reactive particles, the particles being larger in size than foramina of the container. The containers may be selectively reacted with desired materials to synthesize desired sequences of product molecules. As with other methods known in the art, this method cannot practically be used to synthesize a sufficient variety of polypeptides for effective screening.

Other techniques have also been described. These methods include the synthesis of peptides on 96 plastic pins which fit the format of standard microtiter plates. Unfortunately, while these techniques have been somewhat useful, substantial problems remain. For example, these methods continue to be limited in the diversity of sequences which can be economically synthesized and screened.

From the above, it is seen that an improved method and apparatus for synthesizing a variety of chemical sequences at known locations is desired.

## SUMMARY OF THE INVENTION

An improved method and apparatus for the preparation of a variety of polymers is disclosed.

# EXHIBIT R

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on Nov 17 12th 1999
Date: 11/17/99 By: Marilyn Mitchell



File No. 1000.1B3

#34
Arndt. J
11/29/99

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

STEPHEN P. A. FODOR (as previously amended)

Application No.: 08/456,598

Filed: June 1, 1995

For: SIGNAL DETECTION METHODS AND APPARATUS (as previously amended)

Examiner: J. Riley

Art Unit: 1655

AMENDMENT AND RESPONSE

Commissioner of Patents
Washington, D.C. 20231

Sir:

In response to the Office Action of August 17, 1999, (paper no. 31), please make the following amendments and consider the following remarks:

In the Claims:

154. An apparatus for detecting [labelled] labeled nucleic acids, comprising:

(a) a substrate comprising at least 10 different nucleic acids at known locations on the surface of the substrate, each of the known locations having an area of $10^{-2}$ $cm^2$ or less, some of the nucleic acids being bound to said labeled nucleic acids;

1 cont'd.

(b) an excitation light source;

(c) a detector [coupled to said source and] adapted to [received] receive a signal from said label from said surface;

(d) a translator [coupled] adapted to move said substrate relative to said detector; and

(e) a data [storage] collection system [coupled to] adapted to receive input from said detector.

REMARKS

Applicants want to thank the Examiner for participating in the interview of November 4, 1999. At that interview, Applicants explained that Southern is not prior art against the pending claims. Applicants informed the Examiner that the U.S. equivalent of the Southern PCT is U.S. Patent No. 5,700,637, and it does not have an earlier effective filing date (the Interview Summary should have a "not" after "does" in the last line of text). Applicants also raised the Information Disclosure Statement that they filed last August and the Examiner stated that her review has not been completed.

At the interview Applicants provided the Examiner with a non official copy of the priority document which illustrated the support for the portions which related to the Southern reference.

Additionally, Applicants disclosed that the U.S. Southern equivalent of the Southern PCT is being asserted against the Assignee of the present application. See Oxford Gene Technology (OGT) v. Affymetrix, Civil Action No. 99-348-JJF, in the U.S. District Court for the District of Delaware. OGT is also asserting the U.K. equivalent of

the Southern patent (EP) in the High Court of Justice, Chancery Division, Patents Court, HC 1999 No. 02517. OGT has also filed a revocation action against one of Affymetrix' EP patents (EP 619,321) in the same court. EP 619,321 claims an array.

Applicants have performed some minor amendments to claim 154. Two typographical errors were corrected and several words were eliminated in step (c) as they were unnecessary. Step (c) was also amended for clarification and steps (d) and (e) were amended to insert preferred language. The amendments find support at least on pages 40-42.

Applicants note that claim 116 filed with the June 23, 1999, amendment has two occurrences of "on" in line 2 of the claim. This is a typographical error, not an amendment - as the prior version of the claim did not have two occurrences and the extra "on" was not added by amendment.

## DISCUSSION

Applicants have explained to the Examiner that Southern WO89/10977 is not prior art to the present claims as it was published on November 16, 1989. The U.S. equivalent was nationally filed even later (see attached printout from the USPTO database which shows that the Southern U.S. application entered the National Phase on September 28, 1990). Applicant's first priority application, U.S.S.N. 07/3962,901, was filed on June 7, 1989. This application disclosed arrays of nucleic acids and the use of fluorescent labels to detect hybridization before either of the two dates mentioned above (and in much better detail than Southern). As such, the June 7, 1989, filing antedates the

Southern U.S. and PCT patent documents and removes it as a reference. Since Southern is no longer a reference, the current rejection should be withdrawn.

Specific support for nucleic acids/oligomers/nucleotides can be found in U.S.S.N. 07/3962,901on the following pages/lines: 1/11, 1/32, 10/10, 12/29, 13/6, and 27/19. Nucleic acids are clearly contemplated as components of an array. There is support for fluorescent labels as shown on pages/lines: 15/30-31, 22/14, 26/21-27, 27/ 1-3 and 8-11 as well as originally filed claims 17, 22, and 43.

Applicants still assert that Southern does not show or suggest the present invention alone or in combination with other references for at least the reasons stated in the last response. However, it is now unnecessary to rely on that response as Southern is not a reference.

CONCLUSION

Applicants have shown that neither the Southern PCT or U.S. effective dates are prior to Applicants first priority date. Applicants first priority document antedates the Southern subject matter that is cited as relevant by the Examiner. Consequently, Applicants do not need to argue that the Southern reference is not relevant to the present claims as it is not prior art. As such, the present rejection should be withdrawn.

Applicants request that the Examiner reconsider the rejections and remove the rejections. Such action is hereby solicited.

Respectfully submitted,

AFFYMETRIX, INC.

Date: 11/17/99

By: _____
Philip L. McGarrigle
Reg. No. 31,395

Affymetrix, Inc.
Legal Department
3380 Central Expressway
Santa Clara, CA 95051
(408) 731-5000 (phone)
(408) 481-4709 (fax)
phil_mcgarrigle@affymetrix.com

# EXHIBIT S

**Affymetrix Provides Update on Litigation Against Incyte**

Affymetrix, Inc. (NASDAQ: AFFX) reported today that the United States Patent and Trademark Office ("PTO") has issued an "Order to Show Cause" in connection with Incyte's request to declare interferences between the narrower claims of Affymetrix' issued United States Patent No. 5,800,992 (the "'992" or "two color assay" patent) and to the claims of its United States Patent 5,744,305 (the "'305" patent directed to arrays of nucleic acids with more than 400 probes per square centimeter), and a pending patent application licensed to Incyte Pharmaceuticals, Inc. (NASDAQ:INCY).

Vern Norviel, Senior Vice President and General Counsel of Affymetrix stated, "We welcome the involvement of the Patent Office in clarification of Affymetrix' patent rights, as we originally sought to provoke an interference with the Incyte patent when we filed the application that matured into the '992 patent. We believe that the PTO is well equipped to resolve the matters raised by Incyte, and that, following these proceedings, the PTO will have disposed with most, if not all, of Incyte's defenses to our infringement claims against them."

Mr. Norviel noted that the PTO's actions also have the following effects:

- Affymetrix' claim against Incyte based on U.S. Patent No. 5,445,934 (the "'934" patent directed to arrays of nucleic acids with more than 1,000 probes in a square centimeter) was not affected by the interference. Mr. Norviel noted that the PTO specifically rejected one of Incyte's main defenses on the '934 patent, finding that oligonucleotides are the same as polynucleotides;

- As to the '992 two color patent, the broadest claims of this patent (which are infringed by Incyte) are not part of the interference; and

- As to the particular claims that are involved in the patents, Affymetrix was designated as the senior party. Normally the senior party wins an interference because of the heavy burdens of proof on the junior party.

At present, it is not known whether the PTO's action will have any effect on the scheduled hearing of Affymetrix' Motion for a Preliminary Injunction against Incyte, which is set for April 30.

The PTO order requires Incyte to produce all evidence it has asserted in support of its motion and then allows Affymetrix to file an opposition to Incyte's request in order to enable the PTO to determine whether Incyte's evidence is sufficient to warrant a finding that Incyte has made a "prima facie" showing in support of its interference request. Even as to the few claims that are involved in the interference, the normal proceedings will not continue if Affymetrix is able to demonstrate that Incyte's heavy burden of proof has not been met. The PTO order sets forth a timeline for a ruling on these proceedings in late summer 1999, which Affymetrix believes will likely strengthen its patent portfolio.

Affymetrix has developed and intends to establish its GeneChip system as the platform of choice for acquiring, analyzing and managing complex genetic information in order to improve the diagnosis, monitoring and treatment of disease. The Company's GeneChip system consists of disposable DNA probe arrays containing gene sequences on a chip, reagents for use with the probe arrays, a scanner and other instruments to process the probe arrays and software to analyze and manage genetic information. Additional information on Affymetrix and GeneChip technology can be found at www.affymetrix.com . All statements in this press release that are not historical are forward-looking statements within the meaning of Section 21E of the Securities Exchange Act, including statements regarding the Company's "expectations," "beliefs," "hopes," "intentions," "strategies" or the like. Such statements are subject to risks and uncertainties that could cause actual results to differ materially for Affymetrix from those projected, including, but not limited to, uncertainties relating to technological approaches, product development, manufacturing, and market acceptance, uncertainties related to cost and pricing of Affymetrix products, dependence on collaborative partners, uncertainties relating to sole source suppliers, uncertainties relating to FDA and other regulatory approvals, competition, risks relating to intellectual

property of others and the uncertainties of patent protection and litigation. These and other risk factors are discussed in Affymetrix' Annual Report on Form 10-K for the year ended December 31, 1998. Affymetrix expressly disclaims any obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein to reflect any change in Affymetrix' expectations with regard thereto or any change in events, conditions, or circumstances on which any such statements are based. Affymetrix, GeneChip and the Affymetrix logo are registered tradem

Edward M. Hurwitz
Vice President and Chief Financial Officer
(408) 731-5000

Anne Bowdidge
Manager of Investor Relations
(408) 731-5925 arks used by Affymetrix, Inc.

Affymetrix (ticker: AFFX, exchange: NASDAQ Stock Exchange (.O)) News Release - 5/6/99

**Affymetrix Announces Court Decision on Preliminary Injunction and Summary Judgement Motions**

**Santa Clara, CA — May 6, 1999** — Affymetrix, Inc., (NASDAQ: AFFX) announced today that the U.S. District Court for the Northern District of California issued a decision yesterday with respect to motions filed by Affymetrix and Incyte/Synteni in the on-going patent litigation brought by Affymetrix against Incyte/Synteni. The decision entered by U.S. District Judge, Fern M. Smith, which follows a hearing held on April 30th, denied Affymetrix' motion for a preliminary injunction and Incyte/Synteni's motion for summary judgment. Judge Smith's ruling, denying Affymetrix' preliminary injunction motion, was based on her finding that Affymetrix had not yet met its burden of establishing that Incyte/Synteni's invalidity defenses lacked substantial merit and that Affymetrix had not shown that its business was being harmed in an irreparable fashion such that monetary damages could not remedy the injury to Affymetrix. The court noted that the motion for a preliminary injunction may be renewed should the pending interference be decided in Affymetrix' favor.

Judge Smith also denied Incyte/Synteni's motion requesting summary judgement on the invalidity of Affymetrix' claims indicating that these issues were being pursued by Incyte/Synteni in an interference proceeding at the U.S. Patent and Trademark Office and that the court would not engage in a duplicative resolution of the issue.

"Judge Smith's ruling is entirely consistent with her comments at last Friday's preliminary injunction hearing as previously reported," commented Vern Norviel, Senior Vice President and General Counsel of Affymetrix. "We knew that our request for a preliminary injunction was extraordinary but we believe the facts in this case supported our position. We remain confident that we will prevail in this case and look forward to the next steps as we enforce our intellectual property rights in the DNA array field," added Norviel.

Affymetrix has developed and intends to establish its GeneChip® system as the platform of choice for acquiring, analyzing and managing complex genetic information in order to improve the diagnosis, monitoring and treatment of disease. The Company's GeneChip system consists of disposable DNA probe arrays containing gene sequences on a chip, reagents for use with the probe arrays, a scanner and other instruments to process the probe arrays and software to analyze and manage genetic information. Additional information on Affymetrix and GeneChip technology can be found at www.affymetrix.com.

All statements in this press release that are not historical are forward-looking statements within the meaning of Section 21E of the Securities Exchange Act, including statements regarding the Company's "expectations," "beliefs," "hopes," "intentions," "strategies" or the like. Such statements are subject to risks and uncertainties that could cause actual results to differ materially for Affymetrix from those projected, including, but not limited to, ncertainties relating to technological approaches, product development, manufacturing, and market acceptance, uncertainties related to cost and pricing of Affymetrix products, dependence on collaborative partners, uncertainties relating to sole source suppliers, uncertainties relating to FDA and other regulatory approvals, competition, risks relating to intellectual property of others and the uncertainties of patent protection and litigation. These and other risk factors are discussed in Affymetrix' Annual Report on Form 10-K for the year ended December 31, 1998. Affymetrix expressly disclaims any obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein to reflect any change in Affymetrix' expectations with regard thereto or any change in events, conditions, or circumstances on which any such statements are based. Affymetrix, GeneChip and the Affymetrix logo are registered trademarks used by Affymetrix, Inc.

**Affymetrix, Inc.**
Edward M. Hurwitz
Vice President and Chief Financial Officer
(408) 731-5000

Anne Bowdidge

Manager of Investor Relations
(408) 731-5925